The New England
Journal of Medicine

Copyright, 1944, by the Massachusetts Medical Society

Volume 231 DECEMBER 14, 1944 Number 24

SYMPOSIUM ON GALL-BLADDER DISEASE

A PLEA FOR THOUGHT-TAKING IN THE MEDICAL TREATMENT OF CHOLECYSTITIS*

WALTER C. ALVAREZ, M.D.

ROCHESTER, MINNESOTA

WHEN faced by a patient demanding medicine for a disease for which there is no known or logical treatment, the medical profession has always found it easier to give something than to try to explain why nothing is likely to cure or even to relieve the condition. Unfortunately, most patients will not even stop to listen to such frank speech; they believe firmly in the efficacy of medicine and diet, and they know that there are treatments available for every disease. If an honest physician refuses to give them treatment that he thinks is useless, they usually persist until they find someone who will give them a placebo of some kind.

At first glance this seems to be the best way out for all concerned, but actually it is hurtful to the physician, because after prescribing a placebo for a few years he is almost certain to forget that it never had any basis in scienitfic fact. He will come to believe in its efficacy, and if he is a writer, he is likely soon to be listing and even praising the medicine in his articles and textbooks. Then, if someone comes along who questions the logic of its use or its efficacy in practice, he is likely either to ignore the doubter or to become angry with him for his silly caviling.

Throughout the United States today the current medical treatment for cholecystitis is a diet low in fats and a prescription for some proprietary pill containing usually bile salts or bile salts with some cheap laxative, such as phenolphthalein. The two questions that should arise in one's mind are, How logical and scientific are these prescriptions, and do they do any good? In the first place, why should a person with a diseased gall bladder avoid fats? Originally the idea probably was that bile helps in the digestion of fats, and that hence when there is disease in the biliary tract fats should be avoided. Actually, in all cases of cholecystitis without jaundice, the bile is flowing from the liver into the duodenum without hindrance, and in many cases the cholecystogram shows that the gall bladder is still doing fairly well in concentrating the bile. In other cases, the only defect is that in the intervals between meals the bile is not being stored properly in the gall bladder. In this event, it cannot be poured out in the usual concentration to meet the food when it enters the duodenum.

But if patients with cholecystitis frequently suffered from an imperfect digestion of fats, one would expect them often to have diarrhea with fatty stools and a progressive loss of weight, but this is not the case. Most of the patients suffer from constipation, and many digest so well that they gain in weight. My impression, gained from talking to scores of persons who have been on a low-fat diet, is that it did not make much difference in their digestive comfort. Many had a good digestion to begin with, and many of those who suffered with flatulence and a feeling of heaviness in the abdomen said that the secret of avoiding trouble was never to eat a *big meal* or a meal consisting of rich foods of any kind. A few had learned that certain foods like onions, cabbage or raw apples tended to cause trouble, and they had obtained some relief by leaving these foods alone.

Curiously, no one seems to have thought that the patient who has had a nonfunctioning gall bladder removed surgically is no different physiologically from what he was before the operation, and yet after the operation he is generally told to eat what he pleases, and he digests usually everything he eats. No one thinks of putting him on a diet. From this it must be concluded that the indigestion of cholecystitis is usually not due to any lack of concentrated bile in the upper part of the small intestine, and that hence there is no need of always barring fat from the diet.

Another reason sometimes given for the avoidance of fats in the diet of patients with cholecystitis is

*This paper and the two that follow were presented at the annual meeting of the Massachusetts Medical Society, Boston, May 24, 1944.
From the Division of Medicine, Mayo Clinic.

that with a low intake of cholesterin the formation of gallstones may be avoided. There is no evidence in the literature that this precaution is worth taking, but granting that it is in some cases, it cannot be worth taking in the many cases in which the gall bladder is so packed with stones that it would be impossible to get any more in.

A diet sufficiently low in fats and carbohydrates can, of course, help by reducing the weight of the patient if he or she happens to be stout, but there is no reason for expecting this to restore a badly diseased gall bladder to a healthy state. According to some German writers, the restricted diet forced on Europeans by World War I cut down the frequency of colic in patients suffering from gallstones.

Interestingly, it has repeatedly been shown that if one wants to "flush out" the gall bladder by emptying it as thoroughly as possible, the best way to go about it is to give fats such as cream and egg yolk. According to Boyden, Sosman, Whitaker, and others,[1] fats cause the gall bladder to contract more forcibly and to empty more completely than does the magnesium sulfate that has so often been used for this purpose. To be logical, then, it seems that physicians should often be prescribing a diet rich in fats for patients with cholecystitis. To avoid fats in the diet is to invite stagnation of bile in the gall bladder. This favors excessive concentration of the bile, which in turn favors the formation of stones. The sensible thing to do is to have a patient restrict his intake of fat when a trial shows that this makes him more comfortable.

The pill containing bile acids is probably given with the idea that these substances will cause the bile to flow faster, that with this there will be a flushing out of the gall bladder, and that with the flushing there will be a clearing away of infection, and perhaps some washing out of small stones. According to Phibbs, Wigodsky and Ivy,[2] several investigators, among them Taterka, Impallomani and Jankelson and Altman,[3] found that the giving of bile salts results in an increase in the size of the gall bladder, which indicates that with the more rapid flow of bile out of the liver there is an increase in the flow *into* the gall bladder. That there is no great increase in the flow *out* of the gall bladder and therefore no flushing effect with bile acids was shown by Phibbs and his associates when they gave ketochol, a mixture of bile acids, to dogs. There was no sign of any change from normal in the concentration of bile in the gall bladder.

But even if one could produce a greater flow of bile in and out of the gall bladder by increasing the rate of flow down the common duct, it is hard to see how this could help many patients with cholecystitis, because in this disease the infection, when demonstrable, is found not so often in the bile as deep in the muscular wall of the gall bladder. Moreover, any flushing that may be effected can hardly have any influence on stones that are too large to pass through the cystic duct. The flushing of smaller stones into the common duct, if it could be accomplished, would probably do the patient harm rather than good. Certainly, there is no possibility of any flushing in the many cases in which the gall bladder is too badly diseased to have any function, or in which it is packed with stones or sand, or sealed off from the ducts by a stone imbedded in its neck.

Some may ask, "How about the Meltzer-Lyon type of treatment for cholecystitis?" My answer is that I never could see much logic in it and hence I have never used it. So far as I can tell, it has gone out of fashion and is seldom used today.

It would perhaps be best for the mental development of all physicians if they would oftener admit that there is no logical medical or dietary treatment for cholecystitis, especially when bile has ceased to flow easily into and out of the gall bladder, or when the organ is full of stones or its wall is stiffened with scar tissue and full of bacteria.

To those physicians who say, "But our treatment works perfectly in a high percentage of cases," the answer is that the physician who does nothing for his patients with chronic cholecystitis can point to scores of cases in which for years the man or woman has not had a pain or an ache; he, too, is getting beautiful cures. Cholecystitis being the disease that it is, with its tendency to remissions of symptoms lasting twenty years or more, no one can tell when a treatment was responsible for an apparent cure and when it was not. When, as often happens, I see old persons who have "gotten by" comfortably enough, carrying gallstones for ten or twenty or thirty years, I wonder if I should not avoid surgical treatment as often as I can, but when, as also often happens, I see someone who loses his life because a diseased gall bladder was not removed in time, I wonder if I should ever permit a person with definite cholecystitis to go without operation.

Usually, the person whose gall bladder is beginning to cause a good deal of pain and flatulence had better have it out. I recommend immediate operation also to those persons with a bad gall bladder who have to travel much or live in out-of-the-way places where a good surgeon is not available. I am not inclined to recommend operation when there are one or two stones in a functioning gall bladder and the symptoms, if any, are not those of cholecystitis.

* * *

All this is really a plea for thoughtfulness and specialization in the treatment of cholecystitis, and a protest against the unthinking treatment of all cases with the same diet and the same mixture of bile acids and a laxative.

References

1. Cited by Alvarez, W. C. Mechanics of gallbladder. A chapter in *An Introduction to Gastro-Enterology*. 778 pp. New York: Paul B. Hoeber, Inc., 1940. Pp. 440-473.
2. Phibbs, B. P., Wigodsky, H. S., and Ivy, A. C. Effect of oxidized bile salts on gall bladder bile. *Proc. Soc. Exper. Biol. & Med.* **45**: 313, 1940.
3. Cited by Phibbs, Wigodsky and Ivy.[2]

THE SURGICAL ASPECTS OF GALLSTONES

HOWARD M. CLUTE, M.D.,* AND FRANCIS R. KENNEY, M.D.

BOSTON

AMONG lay people and many physicians as well, there is a deeply grounded belief that gallstone surgery is dangerous and is not to be advised until repeated attacks of indigestion, pain and jaundice make it absolutely inevitable. It is our belief, however, that gallstones can be safely removed if the operation is undertaken before complications have occurred. Furthermore, in the great majority of cases of simple or silent gallstones an early elective cholecystectomy is wiser than an operation into which one is forced by the complications of the disease. There is far too great a tendency to worry unduly about gallstone surgery and to forget the dangers that gallstones may produce.

Gallstone surgery is, however, decidedly major surgery, and requires far greater skill than do most surgical procedures in the abdomen. There is no question that the occasional operator can do as much or more harm in operating on the biliary tract than will result from many of the disease conditions he is treating. Strictures of the common duct, duodenal injuries and fistulas, overlooked cystic and common-duct stones — these are some of the penalties exacted by ill-advised attempts at surgery of the biliary tract. It is most important that the surgeon who elects to operate on biliary-tract disease shall be well trained and thoroughly experienced in the technic of the procedure. The dangers of gallstones lie first in the complications that they may produce and secondly in the surgery required for their removal. These dangers can to a large degree be avoided by the performance of operation before complications occur and by a better quality of surgery.

From January 1, 1935, to December 31, 1943, we operated on 356 patients with chronic cholecystitis, with or without gallstones, and its complications. This series does not include 179 patients with other types of biliary-tract disease not immediately related to gallstones who were seen during this period. In Table 1 are listed the types of biliary-tract disease encountered and the operative mortality of each.

The removal of the gall bladder for chronic cholecystitis with stones or with cholesterosis is now a completely safe procedure. In 201 cases in which operation was performed — 178 with and 23 without gallstones — there was only 1 death, a mortality rate for simple cholecystectomy of 0.5 per cent. The cause of this death was never clearly understood, since autopsy was not permitted. The patient was a woman of thirty-five in good condition. The gall bladder was removed for cholesterosis and the common duct was explored; it contained no stones. Death, apparently from shock, occurred fifteen hours after the operation. There was no evidence of hemorrhage. Thus, the only fatality in 201 patients receiving cholecystectomy for uncomplicated disease of the gall bladder was probably due to an unknown error in surgical technic or to a failure to prepare the patient more carefully for operation. The important point is that simple gallstones can be treated safely. The danger of surgery in these cases has been reduced to a minimum by the co-operative efforts of the internist, the anesthetist and the surgical team in their preoperative, operative and postoperative care.

TABLE 1. *Types of Biliary-Tract Disease.*

TYPE OF DISEASE	NO. OF CASES	DEATHS	
		NO.	PERCENTAGE
Chronic cholecystitis:	201	1	0.5
With gallstones	178	0	
Without gallstone	23	1	
Acute cholecystitis	71	5	7.0
Stones in the common duct	84	8	9.5
Totals	356	14	
General average			3.9

No longer is a patient with simple gallstones seen one day and operated on the next. Time is taken to be certain that the symptoms are due to the gallstones and not to some other trouble, such as heart disease. Tests of kidney function and liver function are carried out. If anemia is present, iron therapy and transfusions are given. Extra fluids, glucose and proteins are administered to improve liver function before surgery is undertaken.

The anesthesia in surgery of the biliary tract plays a particularly important role. A gentle, short, easy operation under the complete relaxation of spinal anesthesia appears to be far safer than a long, difficult one under the incomplete relaxation of many other anesthetic agents. We realize that we are particularly fortunate in having an outstanding anesthetist associated with us, to see all cases before operation and to decide with us regarding the operative risk and the best type of anesthesia. If we could not have a trained anesthetist to give spinal anesthesia for gallbladder surgery we should use ether — or postpone the surgery. Spinal anesthesia should not be used in upper abdominal surgery unless it can be given and supervised by an experienced and well-trained anesthetist.

The postoperative use of parenteral fluids, blood transfusions and oxygen and frequent turning of the patient are of great value in keeping the surgical

*Professor of surgery, Boston University School of Medicine; surgeon-in-chief, Massachusetts Memoria Hospitals; surgeon, New England Baptist Hospital.

mortality of gallstone operations low. Each case should be followed by the surgeon himself to make certain that these measures are properly carried out. In this type of surgery routine orders cannot replace individual attention.

We and other surgeons have in the past stated that exploration of the common duct in gallstone surgery does not increase the risk and that it prolongs the hospital stay by only a few days, if at all. This viewpoint we have come to question. There is, of course, no doubt in anyone's mind that the common duct must be opened if there are positive indications for it. In a great many cases, however, there are definite indications that no stones are present in the common duct, and that it should therefore be left alone. Anything approaching a routine exploration of the common duct at the time of a simple cholecystectomy for gallstones should be avoided. Reoperation has been necessary in certain cases to remove stones left — or re-formed — in the common duct, but in every one of these the duct had been explored at the first operation. A secondary choledochostomy has not been necessary in any case in which the duct was not explored at the first operation. We now believe that choledochostomy increases the time of the surgery, opens a viscus that is easily damaged, increases the shock of the operation and the chances of postoperative complications and prolongs the hospital stay. Choledochostomy should be done only when positive indications are present. In one third of the 201 cases of simple cholecystectomy the common duct was explored, but no stones were found.

There is no intention to imply that every patient who has simple or uncomplicated gallstones should have them removed. If the patient is not a good operative risk because of old age, hypertension, heart disease or other constitutional defects, no operation for simple gallstones should be undertaken unless it appears that their removal will improve the patient's general health. As evidence of this belief, there were 81 cases not included in this study, with gallstones or probable gallstones, in which surgical removal was not advised. In all such cases consultation is sought before a final decision is reached.

The two most frequent complications of gallstones are attacks of acute cholecystitis and the passage of stones into the common duct. Seventy-one of these patients had acute cholecystitis, with a 7.0 per cent mortality, and 84 stones in the common duct, with a 9.5 per cent mortality. It is difficult to keep the statistics clear, since in some of the cases of acute cholecystitis there were stones in the common duct as well. The important point is that both the complications mentioned carry a serious mortality risk.

It has long been our[1] contention that most cases of acute cholecystitis begin not with a bacterial infection of the biliary tract but with an obstruction of the cystic duct that interferes with the circulation of the gall bladder. Following this obstruction comes pressure on the veins, the lymphatics and even the arteries, which produces edema, infarction, necrosis and even perforation of the gall bladder. Not until this process is well established — in thirty-six to forty-eight hours — does bacterial invasion occur. Because of this basic course of the disease, immediate surgery within a day or at most two days of the onset of acute cholecystitis and before bacterial invasion occurs is wisest and safest. Delay in these cases means waiting for the onset of infection and for the possibility of perforation of the gall bladder, which occurs in about 20 per cent of the cases.

Operations on patients within twenty-four to forty-eight hours of onset are and should be safe and uncomplicated procedures. Death from acute cholecystitis has occurred in patients who have had repeated attacks of acute cholecystitis that have been "watched." Finally an attack appears that does not subside but goes on to develop infection, abscess formation, cholangitis or perforation and resulting peritonitis. All 5 patients who died from acute cholecystitis had had repeated attacks of the disease, all were between the ages of forty-five and seventy-three, with an average of sixty-one, and all were seen some days after the onset of symptoms — too late for early surgery. The causes of death were coronary infarction in 1 case, peritonitis in 2 cases and septic cholangitis in 2 cases. We are therefore convinced that the factor of delay in operating on patients with acute cholecystitis is responsible for much of the mortality, and that the proper management of these cases is surgery soon after the first attack.

One seldom sees a patient with stones in the common duct who has not had repeated attacks of gallstone colic or acute cholecystitis or both. In fact, when a surgeon operates for gallstones in a patient who has had six or eight or more attacks of colic, he must realize that it will probably be necessary to explore the common duct. Stones in the common duct are a dangerous complication of gallstones, as shown by the fact that 8 of the 84 patients with them died. Each of these patients had had repeated attacks of pain, often over a period of many years. Although 1 patient was only thirty-eight years old, all the others were over fifty-nine and the average age was sixty-three. The causes of death in this group are of some importance. In 3 cases, death followed cardiovascular accidents; in 1, post-mortem examination showed only ileus; in 2, acute generalized peritonitis was found; in 1, gas-bacillus infection had occurred; and in 1, death was apparently due to the so-called "hepatorenal syndrome."

In this group with common-duct stones, other serious disease was often found as a result of the long-standing process. Thus, jaundice was present

in at least 20 per cent of the cases, fever and chills were not infrequent as evidence of cholangitis, and a fistula between the duodenum and the gall bladder was present in 3 cases.

All these facts are strong evidence that there is far too great delay in the surgical removal of gallstones. Such complications occur only in patients who have had gall-bladder trouble for a long time, and represent the end stages of gallstone disease. The degree of permanent kidney and liver damage in the patients who survive surgery cannot be estimated, but it must be a distinct factor in later life.

This study does not include 8 cases of acute pancreatitis, although 6 of these patients had gallstones as well. In some cases there had been repeated attacks of biliary colic that were sufficiently clear to warrant a diagnosis of stones and earlier operation for them. Also excluded are 7 cases with cancer of the gall bladder or bile ducts. What relation, if any, exists between these findings and gallstones is problematic. It is, however, well known that gallstones are present in 65 per cent of patients having cancer of the gall bladder.[2]

We wish to emphasize the point of this paper by briefly reporting a case recently seen on the Surgical Service of the Massachusetts Memorial Hospitals.

The patient, a 73-year-old woman, had had her first attack of gallstone colic 20 years previously, and attacks had continued at varying intervals subsequently. In 1938, a diagnosis of gallstones was made by x-ray study. In 1940, the patient was operated on in this hospital for obstruction of the small bowel due to a gallstone in the ileum. In the postoperative period she developed phlebitis in each lower leg, auricular fibrillation and cardiac failure. After a stormy convalescence she was discharged. One year later attacks of gall-bladder colic reoccurred. In 1943, she was admitted to the hospital because of recurring attacks of upper abdominal pain, chills and fever. Because of a high blood pressure (230/100) and arteriosclerotic heart disease, surgery was not undertaken. Early in 1944, the pains, fever and chills returned and were accompanied by obstructive jaundice. Operation was deemed necessary in spite of the obviously poor risk. A large fistulous opening was found between the gall bladder and the duodenum. Stones were present in both the gall bladder and the common duct. The gall bladder was removed, the stones were taken from the common duct and the duodenal opening was closed. The patient recovered and appears to be well.

How much pain and suffering could have been saved this woman by removing her gall bladder and its stones twenty years ago!

* * *

Analysis of this series indicates that gallstones, even when silent, are potentially dangerous. Simple, uncomplicated gallstones in good-risk patients can be removed with a low mortality rate. Improving the surgical technic and the preoperative and postoperative care will materially lessen the number of operative deaths. When patients have repeated attacks of gallstone colic, the chances of serious complications are great and operative mortality is high. Early operation soon after the onset of acute cholecystitis is indicated by the basic course of the disease and is warranted by the results; it will reduce the chances of stones' passing into the common duct and avoid the serious complications that follow their presence there and the resultant surgery. The removal of simple, uncomplicated gallstones is an extremely safe procedure and should be urged before the complications of gallstones appear.

References

1. Clute, H. M., and Lembright, J. F. Immediate surgery in acute cholecystitis. *New Eng. J. Med.* **218**:72-75, 1938.
2. Judd, E. S., and Gray, H. K. Carcinoma of gall bladder and bile ducts. *Surg., Gynec. & Obst.* **55**:308-315, 1932.

RADIOLOGIC ASPECTS OF GALL-BLADDER DISEASE

MERRILL C. SOSMAN, M.D.*

BOSTON

SINCE the advent of cholecystography in 1924, the diagnosis of gall-bladder disease has become extremely simple and accurate. Its simplicity depends on the limited number of possible diagnoses. Either the x-ray reveals a gall-bladder shadow, or there is no shadow. If there is a shadow, either the gall bladder contains stones or it contains no stones. Occasionally gallstones can be demonstrated in the absence of gall-bladder visualization. In our experience at the Peter Bent Brigham Hospital only 20 per cent of all gallstones are opaque enough to be visible without cholecystography. Compared to the almost infinite number of possible diagnoses in the chest, or the gastrointestinal tract, or even in the bones, the four choices noted above are indeed simple. The variations from normal are few in number, the decision is easy, and the final opinion is frequently categorical, often indubitable.

The accuracy of the x-ray test increases with the attention paid to technical details. One must have good films to make good diagnoses. Nearly all the errors in the radiologic diagnosis of gall-bladder disease can be traced to faults in technic, assuming that the physician who interprets the films has had average experience and possesses good judgment. Under average conditions in any x-ray department doing a considerable amount of diagnostic work, the accuracy of this test approaches 99 per cent. Including borderline cases, in which it is a question of opinion whether the gall bladder is diseased enough to interfere seriously with its function, there is an absolute accuracy of at least 95 per cent. Cholecystography is almost unique in x-ray examinations in that it not only portrays the anatomy of the part under consideration and the consequences of major pathologic reactions but also shows clearly a series of physiologic processes. All other x-ray examinations except one portray anatomic structures and variations caused in them by disease or injury, but little, if any, abnormal physiology. The one exception is intravenous (excretion) urography, and this test is quite similar to cholecystography in concept and execution. The functions of the kidney, however, are so complex and the possibilities of disease, injury and tumor are so numerous that a similar accuracy in diagnosis is not to be expected.

TECHNIC OF CHOLECYSTOGRAPHY

Attention to details and a rigid, precise technic pay large dividends in diagnostic accuracy. Among the first of the important technical factors is adequate equipment — fast apparatus capable of making good radiographs in half a second. This helps to avoid blurring of the gall-bladder image by motion, either from breathing, from peristalsis of adjacent organs or from pulsation transmitted to the gall bladder. A fast, thin Bucky diaphragm is also essential to secure good contrast. A cone centered over the gall bladder helps to increase the contrast by excluding other secondary radiations. The tube should be of fine focus to give sharp detail to the image, such as a 2-mm. focal-spot rotating-anode tube, which at the same time allows the use of 300 or 400 milliamperes of current and a correspondingly short exposure. It is most satisfactory to vary the voltage according to the thickness of the patient's abdomen as measured with him prone on the table. The intensifying screens should be clean and free of grain, and as soon as they become abraded or spotted through wear they should be replaced. There is no excuse for some of the dirty, pockmarked screens in daily use in some offices and departments. Contact between the screens and the film should be checked, since lack of close contact results in a blurred image. A target-film distance of 32 to 36 inches instead of the usual 24 to 28 inches helps to improve detail.

Next in importance to the equipment is attention to the details of the test itself. Considering only oral cholecystography at the moment, the dye (tetraiodophenolphthalein) may be administered in any one of several forms or combinations. We originally used the pure dye in enteric-coated capsules, later changing to an emulsion that was mixed with grape juice to disguise both the purple color and the metallic taste. The dye may be dispensed with a weak acid, such as citric, tartaric or malic acid, and simply mixed with water. In an acid medium the dye is precipitated as an insoluble white salt and goes through the stomach unabsorbed. In the alkaline intestinal tract the dye becomes soluble and is absorbed, passing through the portal circulation to the liver, where it is excreted along with the bile salts. It is too dilute when excreted by the liver to cast a shadow on the x-ray films, so that concentration by the gall bladder is essential in demonstrating the gall-bladder shadow. For this reason attempts to show the common duct after cholecystectomy have uniformly failed except by direct injection of opaque material — called "cholangiography" or "choledochography." The common bile duct may be widely dilated after operation and may retain a considerable amount of bile, but never in my experience has it concentrated the liver bile to a point where it could be demonstrated by radiography. A thorough understanding of the

*Clinical professor of roentgenology, Harvard Medical School; roentgenologist, Peter Bent Brigham Hospital.

above steps is essential in interpreting the results of the test.

Preparation of Patient and Technic of Examination

Cleansing of the intestinal tract by either catharsis or enema adds to the accuracy of the tests by removing feces, gas or undissolved dye, which may overlie or obscure the gall-bladder shadow. A routine catharsis on the day preceding the examination was tried but was soon given up, since it was found that the tetraiodophenolphthalein is in itself a cathartic, probably owing to the phenolphthalein portion. Many patients suffer from diarrhea and some from nausea and vomiting as well, but diarrhea alone has not interfered with a satisfactory visualization of the gall bladder. Obviously, however, if the patient has vomited the dye, enough may have been lost to interfere with the test. This happens particularly in patients with peptic ulcer and those with some degree of pyloric obstruction. Golden[2] recommends administering 6 cc. of paregoric before the meal that precedes the giving of the dye. This undoubtedly promotes the comfort of the patient and may allow more complete absorption of the chemical. We do not agree with Curl,[3] who recommends a high-fat diet for several days before the test to empty the gall bladder. With this procedure there is a larger percentage of unabsorbed precipitated dye remaining in the intestines, particularly when the fat is given during the meal just preceding the administration of the dye. Theoretically this should empty the gall bladder and prepare it ideally for the storage of the bile that contains the dye. Actually it seems to interfere with the absorption of the chemical, perhaps through combination of fatty acids and tetraiodophenolphthalein to form an insoluble compound. Antonucci[4] recommends a high-carbohydrate intake before cholecystography on the theory that a large glycogen reserve in the liver improves its excretory function. We have had no experience with this preliminary preparation.

The standard procedure, therefore, is to give 3.5 gm. of tetraiodophenolphthalein after a fat-free evening meal, the exact procedure depending on the type of preparation employed. Many hospitals are now using the double-dose technic, giving one dose of 3.0 or 3.5 gm. after a fat-free noon meal and a similar dose after a fat-free evening meal. This has definitely added to the accuracy of the test, with fewer doubtful or faint gall-bladder shadows resulting. After the evening meal and the dose of the dye, the patient should have nothing to eat or drink except water, fruit juice or black coffee until after the x-ray films are taken, usually at 9.00 the following morning. There is no evidence that limitation of fluid intake increases the concentration of the bile as it is excreted from the liver or that increased fluid intake promotes the flow of bile from the liver, so that fluids need not be withheld as in excretion urography. It is advisable to take a large film of the right abdomen first, at least an 11-by-14-inch film, develop it immediately and view it wet, to locate the gall-bladder shadow. If there is gas or fecal material over the usual gall-bladder area, a cleansing enema — at least 2000 cc. of tap water or normal saline solution — should be used to remove it if it is in the colon, or a drink of water if there is air in the descending duodenum, which may obscure or confuse the findings. The films are best made with the patient prone, the right hand above the head, the face to the right and the right side of the abdomen raised slightly from the table. This position helps to uncover the gall-bladder shadow, particularly in long, thin patients, by rotating the spine slightly to the left and the gall bladder slightly more to the right, rendering the latter less apt to be concealed by the vertebras. The position of the gall bladder varies tremendously. In the obese or thick-set patient of hypersthenic type it may be at the lateral edge of the liver as high as the tenth rib. In the long, lean hyposthenic patient it may lie over the sacroiliac joint or even reach the brim of the pelvis, and not infrequently it is hidden by the spine unless the position described above is used. In exceptional cases it may be necessary to take films with the patient lying face up, with the body rotated to the right to uncover the gall-bladder shadow either from the spine or from gas in the hepatic flexure. Films in the upright position are occasionally of critical value, as will be shown later. If repeated cleansing enemas are not successful in removing troublesome gas from the gall-bladder area, either the supine technic should be tried or 1 cc. of Pitressin should be given hypodermically, provided there is no contraindication to its use. A satisfactory scout film should include the lower half of the liver shadow and the upper half of the innominate bone, as well as the lumbar spine. In viewing the wet film one should identify the liver edge, the kidney shadow, the iliopsoas shadow and the properitoneal line laterally. Occasionally the overlapping of liver and kidney shadows produces a zone of increased density, which to the uninitiated seems to be the gall-bladder shadow. In 2 routine cases the air-filled fundus of the stomach was recognized in the area where the liver shadow should have been, indicating a situs transversus. In both cases, films of the *left* upper quadrant demonstrated a normal gall-bladder shadow and averted a serious error in diagnosis. If the shadow is visualized satisfactorily, at least three films are taken, with a cone centered over the area where the gall bladder lies. It has been found advantageous to take these films with slight variation in rotation, and one of them at least at the end of expiration. This often helps one to decide whether overlying shadows, either so-called "positive" or "negative," maintain a constant relation to the gall-bladder shadow, thus aiding in differentiating bubbles of air or

gas and calculi. If these films are technically satisfactory, the patient is given a fat meal, — two eggs, buttered toast and coffee with cream or an eggnog containing two eggs and some cream, — and at least two more films are taken an hour later, using the same position and technic as for the first set of films. If the first films show questionable shadows that may be those of calculi, two films should be taken in the upright position to demonstrate a change in the position of the calculi. Eliasz,[5] in 1932, was the first to show that some gallstones float in the opaque dye-filled bile, whereas most of the calculi sink to the fundus of the gall bladder when the films are made with the patient erect. This was confirmed and amplified by Akerlund.[6] The floating phenomenon is an extremely interesting and useful test, frequently changing the final diagnosis from a doubtful to an indubitable one. The stones that float at a given level in the upright position are always the cholesterol or "negative" calculi, and the phenomenon is based on the fact that there is a difference between the specific gravity of the bile in the fundus of the gall bladder, which has been there longest and is therefore the most concentrated, and that of the bile in the neck of the gall bladder, which has come more recently from the liver and is less concentrated and therefore of lower specific gravity. The cholesterol calculi simply seek their own level of specific gravity, and they usually lie in a single horizontal plane, causing a dark streak across the opaque white gall-bladder shadow.[7] Frequently the separate calculi are recognizable. It is conceivable that if there were two different kinds of calculi, there would be two separate and distinct horizontal rows in the upright position, but I do not remember having seen this actually demonstrated by x-ray. Nearly all the calculi we see are of the same type or kind in a given gall bladder, and most of the cholesterol calculi were probably laid down in a single shower. Many of them also are seen in gall bladders that concentrate and empty well, so that they must have been made through a physicochemical process at a time when the gall bladder was normal or nearly normal, at least in function. The opaque crystalline pigment calculi also frequently occur in normal gall bladders, but the laminated calculi and those with dense margins around a cholesterol nucleus are oftener found in badly diseased gall bladders, and recurrent infection has probably played a part in their formation. Only the small negative or pure cholesterol calculi float, and the bile must be well concentrated and quite opaque to present this phenomenon. By far the larger majority of calculi, including all the "positive" ones, sink to the fundus of the gall bladder in the upright films, forming a layer of debris at that point. This is just as valuable, however, in identifying them as biliary calculi as is the floating phenomenon across the middle of the opaque gall-bladder shadow.

The films taken an hour after a meal or after the eggnog should also be developed at once and viewed wet before the patient leaves the department. If there has not been at least a 50 per cent decrease in the size of the shadow, further films should be made an hour or two later. The significance of a persistent gall-bladder shadow that does not decrease in size after a meal is discussed below. A proprietary mixture of concentrated lipoids, such as Cholex (National Synthetics Company), is available, and this may be used in place of a fat-containing meal. Its chief advantage is its small bulk and its ease of preparation. It is particularly useful for patients who do not like eggs and for those who are nauseated by the thought of food.

The entire examination as a rule takes only slightly over an hour and requires only two sets of films, as described above — one set fifteen hours after taking the dye and the other at least an hour after the test meal. We originally made several sets of films during the day,[8] the patient fasting in the meantime, to demonstrate progressive increase in the density of the shadow as an index of normal concentrating power. After twenty years of experience, we know the expected standard of density at the fifteen-hour examination, and believe that it is unnecessary to prolong the examination beyond the two sets of films, except in case no gall-bladder shadow is demonstrable at the first examination. It has been our custom to check each case of nonvisualization by intravenous injection at a subsequent date. Most roentgenologists, however, prefer to repeat the oral method, and if this is done it is advantageous to do it the following day, the patient being on a fat-free diet the entire time. This obviates hospitalization, which should be done for intravenous injection, and avoids the risks of reaction from the injection, both local and systemic. If any of the dye gets into the tissues around the vein being injected, an intense local reaction is set up. Some patients have had thrombosis of the vein after injection, a few have had acute coronary attacks, and several sudden deaths have been reported after intravenous injection of tetraiodophenolphthalein. Systemic reactions are less apt to occur if the dye is injected slowly — over a period of at least fifteen minutes. Because of these possible reactions many x-ray departments have abandoned the intravenous method entirely and rely on the oral method, using the double dose either routinely or as a check on the single dose if nonvisualization of the gall bladder occurs. In either case a small percentage of patients show a normal gall-bladder shadow at the second examination, when none was seen the first time. This varies from 2 to 10 per cent in different clinics. Many of these shadows are probably the result of errors in technic, either by the patient, who perhaps misunderstood the directions or willfully disregarded them, or by the radiographer, who did not pay attention to the details

listed above. A careful, conscientious, well-trained x-ray technician is an invaluable asset, particularly in this field.

There is a third possibility to be considered — that the gall bladder is visualized but with a shadow fainter than normally expected at the given time. In such cases it is wise to repeat the examination, using either the intravenous method — if there is no suspicion of coronary disease — or the double-dose method. Tracey[9] strongly advises checking all collateral organic systems — by a gastrointestinal series, a barium enema and so forth — and trying symptomatic treatment for a short period before rechecking the gall bladder, intimating that there may be physiologic variations that interfere with the test. He states that if the symptoms are relieved by treatment there may be good visualization of a previously faint or nonvisualized gall bladder. Lahey and Jordan[10] go so far as to state that of patients with chronic dyspepsia and nonvisualization of the gall bladder 44 per cent show normal gall-bladder shadows after satisfactory bowel management. Our series has shown no such discrepancy. This is certainly true, however, in the case of jaundice. No harm has followed if the dye is given either intravenously or orally in jaundiced patients, but almost invariably there is nonvisualization of the gall bladder. A good shadow is occasionally obtained when the jaundice is clearing or it is due to hemolysis and not to obstruction. It is much better, however, to wait until the jaundice has entirely cleared before doing a cholecystography. There is no danger in trying it, but it constitutes a waste of time, material and money.

It is of course obvious that if pyloric obstruction or prolonged pylorospasm is present, the dye may be retained in the stomach unabsorbed, in which case nonvisualization obviously results. This complication can be recognized by identifying the finely mottled opaque shadow of the dye in the stomach. In a recent case of this type further gall-bladder films twenty-four hours later revealed passage of all the dye from the stomach and a normal gall-bladder shadow,whereas there was no shadow before. Such a complication may explain the discrepancies noted above between the results reported by Lahey and Jordan and our figures.

Fluoroscopy has not been used routinely in our department since the first days when we were repeating Graham and Cole's experiments,[11] and only a few roentgenologists now use fluoroscopy as part of cholecystography. We found it to be of no help in the clinical examination, and now use it only in an occasional patient when spot films in the upright position are desired. Good films give much more information, especially concerning detail, than can be expected from fluoroscopy. The information obtained by fluoroscopy about changes in shape and in position with palpation and change in posture is not of enough importance to justify the time consumed by the method.

Recently a new drug has been found that also renders the gall bladder opaque some hours after ingestion. This substance is in no way related to tetraiodophenolphthalein, and it is less apt to cause some of the uncomfortable side effects such as nausea, vomiting and diarrhea. Originally described in Germany as "Biliselectan,"[12] it is *beta*-(4-hydroxy-3,5-diiodophenyl)-alpha-phenyl-proprionic acid. It is dispensed as a 0.5-gm. tablet, and is taken by mouth with sips of water, lemonade or weak tea after a fat-free evening meal, just as in the oral method with tetraiodophenolphthalein. So far, after use in about 150 patients, it has shown several distinct advantages over tetraiodophenolphthalein. There is definitely less toxic reaction, such as nausea, vomiting and diarrhea, in the gastrointestinal tract, and there is usually little if any opaque residue in the bowel to obscure the gall-bladder area. The drug is excreted largely through the kidneys, and a few patients complain of mild burning on urination the morning after taking the tablets. In this country it is manufactured by the Schering Corporation under the trade name of Priodax and by the National Synthetics Company as Dikol. We have been using it routinely since preliminary clinical tests demonstrated its advantages. The standard dose is 3.0 gm. (six tablets). Double doses have frequently been given without untoward results and with excellent visualization of the gall bladder at fifteen hours, with as dense a shadow as any seen following intravenous administration of tetraiodophenolphthalein. In fact, the shadow is often so opaque that small stones may be entirely hidden. This chemical has not been accepted for intravenous injection. It will probably replace the various forms of tetraiodophenolphthalein preparations in most x-ray departments for oral use.

Interpretation of Results

The facts that may be demonstrated by cholecystography are the size, shape and position of the gall bladder, the degree of filling and the relative concentration, the presence or absence of shadows indicative of calculi and the amount of emptying, as revealed by a decrease in size, usually one hour after a fat-containing meal.

The size, shape and position of the gall bladder are extremely variable. A small gall bladder, if of normal density, does not indicate inability to fill normally; rather it suggests that the patient has partaken of forbidden food. A large gall bladder is of no clinical importance unless there is lack of concentrating power or other evidence of disease. A markedly distended gall bladder, if due to obstruction anywhere in the biliary tract, either fails to fill with the dye or does not concentrate it. A gall-bladder shadow of normal density for the given

method should therefore be considered normal regardless of its size, if the other findings are also normal. The position of the gall bladder depends on the habitus of the patient, as noted above. Changes in position alone are of no value in interpretation, unless the cause of displacement can be demonstrated. Situs inversus should always be kept in mind because of the possible error in interpretation as a case of nonvisualization. Changes in shape, however, are occasionally important, usually as an indication of fixation or adhesions by extrinsic disease. In actual practice this is rare unless there is a history of surgical drainage of the gall bladder. Most of the dense adhesions found at operation cannot be demonstrated or even suspected by x-ray examination. It must be remembered that one is viewing a three-dimensional object in only two dimensions and that any abnormal or peculiar shape must be interpreted accordingly. The fundus of the gall bladder is frequently seen partly overlapping the body of the shadow. This is as a rule not due to adhesions but to the free portion's folding over the portion that is normally fixed to the undersurface of the liver. Rarely the gall bladder is more or less divided into two or three compartments by either transverse or oblique bands. These may be either partial septums in the wall of the gall bladder — usually in the mucosal layer — or bands compressing it extrinsically. In either case, the finding is of little or no importance per se. Such gall bladders usually fill, concentrate and empty to a normal degree, and the few patients in this series that have been operated on without other indications have not had their symptoms relieved by cholecystectomy.

The filling of the gall bladder with dye-laden bile obviously depends on its ability to empty. If it cannot empty, there is poor filling and a faint shadow or no filling with fresh bile and no shadow. In either case the interpretation is based on the density of the shadow and is inseparable as a fact from the observations based on lack of concentration. If there is no visualization of the gall bladder by opaque material, the logical and correct interpretation is a nonfunctioning gall bladder.*

If the radiographic technic has been above criticism and the patient has faithfully followed directions, this is a very reliable finding. In 90 per cent of nonvisualized gall bladders in our series gallstones have been found at operation. The accuracy of this finding alone is close to 99 per cent, in terms of grossly pathologic gall bladders, particularly if the examination has been repeated either by intravenous injection or by the double-dose technic and the finding has been verified. Much less reliable, however, has been the demonstration of a poorly functioning gall bladder or a faint shadow, particularly by the single-dose oral method. Gross pathologic changes were found at operation in only 75 per cent of those in this group who came to operation. A cholecystographic examination giving this finding without calculi should of course be repeated, preferably by intravenous injection, so that all question of failure of absorption of the dye can be eliminated. So far we have found fewer errors in this group with Priodax, particularly with the double-dose technic. If the symptoms are not characteristic or acute, it may be wise to delay the second examination for several weeks, as Tracey[9] suggests. On the whole, if a shadow of fair to good density results, no calculi are found and the gall bladder empties promptly and well, it is safer to class the result as within the normal range rather than to try to estimate the shadows of fair density in terms of moderate degrees of cholecystitis.

It should be noted that our results are not based on histologic examination of the excised gall bladder alone. Autopsies have shown that 60 per cent of people over forty years of age have noncalculous cholecystitis, but mostly of mild degree and of doubtful significance as regards the production of distressing symptoms.[13] Most if not all of this mild cholecystitis would be classed by us as no more than normally expected, and if no gall-bladder shadow were obtained in such a patient we should consider it an error rather than a success.

The radiographic demonstration of calculi, however, is the most reliable finding of all, and the most significant to the patient, the physician and the surgeon. In our series this finding in patients coming to operation has been accurate in over 99 per cent and there have been several years when it has been 100 per cent correct. Many patients in whom gallstones have been reported do not have the finding either verified or disproved, and this leaves a possible source of error, since they are apt to be the ones with milder symptoms. If the x-ray films are of excellent quality and if calculi, either positive or negative, are demonstrated, there should be no more than a 1 per cent chance of error. The causes of these errors are discussed below. It must be emphasized, however, that not all gallstones can be visualized, since there are many cases of calculous cholecystitis in the cases with nonvisualized gall bladders in which the calculi are not radiopaque. Of all the cases coming to operation in which gallstones were found, calculi were positively reported in only 75 per cent. The others not identified preoperatively, however, were reported as nonfunctioning or pathologic gall bladders, and as noted above we have learned that 9 out of 10 patients in this group are found at operation or autopsy to have biliary calculi. The routine films taken one hour after the meal have been helpful in securing this

*The results of cholecystographic examination should not be reported as "positive" or "negative." To one person the report "The Graham test was negative" means that a normal gall bladder was found. To another it may mean that the results were negative; that is, that no gall-bladder shadow was seen. It is better to choose words that allow of no misunderstanding or misinterpretation — for example, "nonvisualization of (nonfunctioning) gall bladder," "cholelithiasis" and "poor concentration."

high degree of accuracy, since the decrease in the size of the gall-bladder shadow has several times uncovered small calculi hidden in the opaque bile. Upright films in doubtful cases have added to the accuracy. The interval of time between the two sets of films and sometimes the slight shift in position of the gall-bladder shadow owing to food in the stomach and duodenum have also occasionally helped to decide that a questionable shadow was outside the gall bladder and not a biliary calculus.

The demonstration of biliary calculi radiographically should not be accepted as the chief indication for surgical intervention. It should, however, be accepted as an extremely trustworthy finding on which a decision to operate may be based. In my experience the patients with calculous cholecystitis and biliary symptoms have experienced a high degree of relief following cholecystectomy, whereas those without calculi have frequently shown no clinical improvement after removal of the gall bladder. The percentage of cholecystectomies for noncalculous cholecystitis could be used as a check on the conservatism and judgment of the surgeon. In this hospital and in the series of 1032 consecutive cholecystectomies reported by Wilkinson,[14] 90 per cent showed gallstones.

It must be emphasized that x-ray examination of the gall bladder, or of any organ of the body, does not explain symptoms. Gallstones may be silent for long periods of time. The demonstration of calculi in the gall bladder is a factual finding, but their relation to the patient's symptoms is quite another problem, and if there is a discrepancy the referring physician should have the other organs or systems investigated.

The emptying of the gall bladder in response to the specific demand from certain foods is of doubtful value in diagnosis. Certainly if the gall bladder does contract normally, — at least a 50 per cent decrease in volume in one hour, — this response can be considered as an added index of normality. Not infrequently, as noted above, the changes in size, shape and position are helpful in other ways. In many cases the contraction of the gall bladder forces the more opaque bile into the cystic and common ducts so that they can be clearly outlined and studied. The tortuous course of the dye in the neck of the gall bladder through the valves of Heister should be recognized, and not misinterpreted as calculi or polyps. Not infrequently a calculus in the cystic duct can be located in this way. If, however, the gall bladder fails to respond to the fat meal and does not decrease in size, little or no importance can be attributed to this finding. In the great majority of patients the delay in emptying is physiologic and of no clinical importance. Obviously if the patient has pylorospasm and the fat meal does not get into the small intestine, there will be no absorption and no contraction of the gall bladder. I have seen this sequence of events from nausea, headache, pain, emotion and many other causes. When we[1] were experimenting with various foods in an attempt to determine their relative effect on the emptying time of the gall bladder, we noted that a cupful of olive oil gave an immediate and marked response in an Italian patient, who considered it a tasty drink. A similar dose, however, had no effect on the gall bladder of the next patient, one of Scottish-Irish extraction, in whom nausea and probably pylorospasm were the only results. Inasmuch as normal pancreatic secretion is essential to the digestion and absorption of fats, we at first thought that failure of emptying of the gall bladder might be due to pancreatic deficiency. This may be an occasional cause, but this is not a reliable method of indicating it. Rigler[15] states that failure to empty indicates poor function of the gall bladder or valvular obstruction of its neck, and Golden[2] says that lack of contraction may be due to a thick-walled gall bladder or to debilitating conditions, and in 1 case was due to tuberculous peritonitis. In my experience, however, it is better to discard this finding as an index of gall-bladder disease unless there is irregularity of outline or rigidity of the walls, which would support the finding and at the same time explain it by pericholecystic disease or tumor.

Errors in Interpretation

Holmes[16] rightly states that variations in the density of the gall-bladder shadow are due to faulty technic oftener than to disease. This assertion might well be expanded by saying that errors in interpretation of all sorts, including faintness of the shadow, are due to errors in technic oftener than to failure of the test itself.

Some of the possible errors have already been pointed out. Another source of error is in reality due to a failure of the test, since it has been shown that a moderate degree of chronic cholecystitis or even an acute cholecystitis is compatible with normal function and a normal cholecystographic shadow. Cholesterosis, or so-called "strawberry gall bladder," may be present and not interfere with gall-bladder function as demonstrated by this test. Several times, however, we have noted a fine irregularity in outline of a normally opaque shadow, due to diffuse cholesterosis of the mucosa of the gall bladder but not interfering with its function. Gas, either in the colon or in the descending duodenum, has been the greatest cause of error. Either the stones were hidden or obscured by overlying gas or a persistent bubble of gas was interpreted as a calculus. Motion due to breathing during the exposure is another frequent source of error, since it may blur out the shadows of calculi. This is a particularly important factor in large charity hospitals and teaching clinics, in which many patients do not speak or understand the English language. It is a constant source of wonder that many people do not know how to hold their breath even for one

second. This is an additional reason for having the films made with as short an exposure as possible. An occasional kidney stone may simulate a gallstone, but oblique or lateral films practically always separate the two organs. An occasional explanation of error lies in the fact that patients sometimes pass their stones, either through the cystic and common ducts or by direct ulceration into the duodenum. Small calculi may be hidden by the opaque bile, but they should be seen in films of the partly emptied gall bladder or in upright films. Occasionally a gall bladder full of milk-of-calcium bile may simulate a normal cholecystogram. This error can be avoided by taking films before the dye is given or by repeating the films a week later without the dye. Usually such a shadow has a granular appearance, which is easily recognizable if the films are of excellent quality. Nonvisualization may be the result of lack of absorption of the dye from the intestinal tract or in rare cases to liver disease, either tumor or metastases, cirrhosis or chronic passive congestion. In a very few cases there is congenital absence of the gall bladder.

Overlapping shadows may be erroneously interpreted as calculi; thus, a small calcified hydatid cyst or even a Ghon tubercle deep in the posterior costophrenic sinus, which, in an obese or broad-chested patient, may actually overlie the gall bladder when the films are made in deep inspiration, may cause confusion. If one film is taken at the end of expiration this mistake can be avoided. Anomalies of the gall bladder are rare. An occasional diverticulum of the gall bladder is found, but oftener the supposed diverticulum is due to a septum in the wall of the gall bladder. Papillomas or adenomas of the gall bladder may simulate calculi. They are usually single, are rarely over 0.5 cm. in diameter and are marginal in location, according to Kirklin.[17] They can be seen only or best on the films made after partial emptying. Upright films are most important in their accurate identification, since these shadows do not change position as would stones. Papillomas, polyps and adenomas are of course recognizable only in dye-filled gall bladders. Their possible relation to cancer of the gall bladder is highly questionable. Theoretically it is possible to diagnose an early carcinoma of the gall bladder by cholecystography, but so far I do not know of its having been done. It is probably wise to remove the gall bladder, however, when papillomas are demonstrated, just as it is wise to urge cholecystectomy when biliary calculi are revealed.[18]

The presence of cholecystitis in either an acute or a mild chronic stage and with a normal gall-bladder shadow has already been mentioned as an error in diagnosis. The clinical importance of a so-called "mild chronic cholecystitis" is doubtful. If these cases are excluded, there will be a high accuracy in the confirmed diagnosis of normal gall bladder, although it is hardly fair to accept the diagnosis as confirmed if the gall bladder is not removed. Small gallstones may be missed by palpation alone during operation.

Occasionally small stones or gritty particles like sand are found in the gall bladder at operation when the shadow appeared quite normal. This was quite rare in our experience. Others have reported this finding in 5 per cent of cholecystographically normal gall bladders. The more attention is paid to technical details, the smaller this percentage will be, particularly if upright films are taken routinely, as is now being done in some clinics.

Before cholecystography was announced by Graham and Cole,[11] much emphasis was placed on the so-called "indirect signs" of gall-bladder disease. A presumptive diagnosis of gall-bladder disease was often made, based on slight deformities of the duodenal bulb, pressure effects on the duodenum, irritability of the duodenal cap and pylorospasm, or any of these signs alone. As now known, these alleged diagnoses were mostly guesswork, and little if any attention is now paid to these minor physiologic or anatomic changes when considering gall-bladder disease. Only rarely does the diseased gall bladder cause deformity of the duodenal cap, and the diagnosis of adhesions from the gall bladder is extremely infrequent. Occasionally, however, it can be made accurately and logically, particularly when there is a fistula between the duodenum and the biliary tract. This occurs oftenest as the result of ulceration of a stone or stones from the gall bladder into the duodenum, less often by perforation of a duodenal ulcer into the common bile duct, and even less frequently as the result of a carcinoma of the papilla with incompetence of the sphincter of Oddi. The rupture of gallstones into the duodenum occurs most frequently in old women, and if the stone is large enough, it may cause obstruction of the small bowel, usually near the ileocecal valve. Gallstone ileus can be promptly diagnosed by demonstrating the calculus in the obstructed small bowel, by noting air or gas in the gall bladder or biliary tract or by demonstrating the fistulous connection with barium. Films of the abdomen taken for intestinal obstruction or acute abdominal symptoms should always include at least the lower half of the liver, and the roentgenologist should always look for air in the common or hepatic ducts. One sees only what one looks for, and it is wise to train oneself to look for streaks of air in the liver shadow. The disappearance of calculi, particularly large calculi, previously known to have been in the gall bladder is presumptive evidence of perforation or rupture of the gall bladder. Smaller calculi may be passed into the duodenum through the intact cystic and common ducts. This may account for an occasional error in diagnosis when gallstones demonstrated by x-ray are not found at operation, particularly if the operation is done some time after the x-ray examination. The passage of calculi from the

gall bladder directly into the duodenum is probably more frequent than statistics indicate, since we usually see several cases a year. Frequently the stones are passed uneventfully in the stools. Occasionally they are vomited — a dramatic method of demonstrating gallstones. The fistulas may heal spontaneously, whereas with others there is a prolonged period of intermittent chills and fever, frequently without jaundice. Rarely if ever can a normal gall-bladder shadow be found by cholecystography after such a spontaneous perforation, but cases have been reported in which subsequent crops of gallstones have formed.

There is one condition in which an erroneous diagnosis of gallstone ileus is sometimes made. There may be concretions or calculi in the appendix that exactly simulate gallstones — laminated, faceted ring shadows that are in reality appendicoliths. If there is an associated ileus from acute appendicitis or peritonitis, the calculi may be interpreted as being in the terminal ileum and as causing obstruction of the small bowel. There is no air in the biliary system, however, in such a case, and that should put one on his guard.

Fistulas from the gall bladder may also lead to the stomach, to the colon, to other parts of the small bowel and even through the diaphragm into a bronchus. In any case with biliary fistula the gall bladder cannot be visualized by cholecystography, but on rare occasions it can be visualized by a barium meal or by a barium enema.

The direct demonstration of opaque or positive gallstones by x-ray films without cholecystography is quite reliable and rarely needs to be confirmed by the Graham test. Occasionally renal calculi simulate the typical ring shadows or faceted appearance of gallstones, particularly if they are formed in a hydronephrotic, pyonephrotic or polycystic kidney. Oblique films, lateral films or those made in different phases of respiration usually suffice to differentiate them. Occasionally it is necessary to do both cholecystograms and pyelograms to be sure where the calculi are located. Calcified lymph nodes are occasionally mistaken for gallstones, but fortunately they are rare in the gall-bladder area. Biliary-pigment calculi may look very much like calcified nodes, so that the reverse error is also possible, and has been made. When the cystic duct is completely obstructed, the gall-bladder mucosa may excrete calcium into the bile[19] and form milk-of-calcium bile, which may exactly simulate a normally dense gall-bladder shadow. It may form a calcified cast of the gall bladder, or the calcium may be deposited in the wall of the gall bladder. These complications can be recognized by plain films of the gall-bladder area before cholecystography.

Cholangiography is a valuable method of examination when stones in the common bile duct are suspected. If it is done during operation, using a portable x-ray apparatus, it is classed as "immediate"[20]; if it is done several days or more after operation, it is spoken of as "delayed."[21] The latter is much to be preferred, since it can be done under fluoroscopic observation and control, with spot films as indicated. The size, shape, location and direction of the common duct and hepatic duct can be demonstrated, obstructions located, patency determined and emptying into the duodenum observed. We prefer to use lipiodol or Iodochloral, but Thorotrast or Diodrast can be successfully employed. The opaque material is injected slowly through the drainage tube or T tube, using very gentle pressure, and its progress is carefully watched on the fluoroscopic screen. If an obstruction or a filling defect is encountered, spot films are made at once, since small calculi or debris may be covered up by too much opaque material. It is not always possible to differentiate calculi in the common duct and bubbles of air or small blood clots. In the latter case re-examination several days later may give perfectly normal results. Not infrequently one or more of the pancreatic ducts are visualized if they empty into the common duct. Cholangiography is probably of the greatest usefulness when there is a question whether it is safe to remove the drainage tube. It is invaluable and essential when such operations as reconstruction of the common bile duct have to be done.

Summary

Cholecystography is a simple, safe and extremely accurate method for the study of the gall bladder.

Good films are necessary if good diagnoses are to be made. Films of exceptional quality give the greatest accuracy. The utmost attention to technical detail pays dividends in diagnostic correctness.

The positive diagnosis of gallstones or of a nonfunctioning gall bladder should be correct in 99 per cent of the cases.

A new chemical (Priodax), not related to tetraiodophenolphthalein, has been tried successfully and is thought to be superior in routine oral examinations of the gall bladder to chemicals previously used.

The details of radiographic technic and the principles of roentgenologic interpretation are discussed.

721 Huntington Avenue

References

Between February, 1924, when Graham and Cole's original article appeared, and September 30, 1943, eight hundred and sixty-four articles on cholecystography have been listed in the *Cumulative Index*. It is impossible and unnecessary to list them all, so that only the ones referred to in this article are subjoined. Many important and valuable papers are omitted, and their lack of inclusion does not reflect on their value.

1. Sosman, M. C., Whitaker, L. R., and Edson, P. J. Clinical and experimental cholecystography. *Am. J. Roentgenol.* **14**:495-503, 1925.
2. Golden, R. *Diagnostic Roentgenology*. 600 pp. New York: Thomas Nelson & Sons, 1941.
3. Curl, H. High fat diet preceding cholecystography: review of literature and experimental studies on filling normal gallbladder. *J. A. M. A.* **119**:607-610,1942.
4. Antonucci, C. La cholécystographie rapide *Presse méd.* **40**:983-986, 1932.
5. Eliasz, E. Neuere Gesichtspunkte bei der röntgenologischen Funktionsprüfung der Gallenblase. *Fortschr. a. d. Geb. d. Röntgenstrahlen* **46**:402-413, 1932.
6. Akerlund, A. Beobachtungen bei Cholezystogrammen in aufrechter Körperstellung: ein neues röntgenologisches Gallensteinsymptom. *Acta Radiol.* **14**:74-81, 1933.

7. Ettinger, A. Visualization of minute gall stones. (Layer formation of bile.) *Am. J. Roentgenol.* **35**:656-661, 1936.
8. Whitaker, L. R., Milliken, G., and Vogt, E. C. Oral administration of sodium tetraiodophenolphthalein for cholecystography. *Surg., Gynec. & Obst.* **40**:847-851, 1925.
9. Tracey, M. L. Surgery in cases of faulty visualization or nonvisualization of gallbladder. *Surg. Clin. North America* **23**:669-672, 1943.
10. Lahey, F., and Jordan, S. M. Management of biliary tract disease. *Am. J. Surg.* **11**:1-5, 1931.
11. Graham, E. A., and Cole, W. H. Roentgenologic examination of gallbladder: new method using intravenous injection of tetrabromphenolphthalein. *J. A. M. A.* **82**:613, 1924.
12. Dorn, M., and Diedrich, P. Ein neues Roentgenkontrastmittel der Gallenblase. *Deutsche med. Wchnschr.* **66**:1133, 1940.
13. Cattell, R. B., and Kiefer, E. D. Failures after cholecystectomy. *J. A. M. A.* **93**:1270-1275, 1929.
14. Wilkinson, S. A. Chronic cholecystitis versus irritable colon. *J. A. M. A.* **109**:1012-1016, 1937.
15. Rigler, L. G. *Outline of Roentgen Diagnosis: An orientation in basic principles of diagnosis by roentgen method.* Second edition. 338 pp. Philadelphia: J. B. Lippincott Company, 1943.
16. Holmes, G. W., and Ruggles, H. E. *Roentgen Interpretation.* Sixth edition. 364 pp. Philadelphia: Lea & Febiger, 1941.
17. Kirklin, B. R. Cholecystographic diagnosis of papillomas of gallbladder. *Am. J. Roentgenol.* **25**:46-50, 1931.
18. Cheever, D. Innocent gall stones and harmful cholecystectomy? *New Eng. J. Med.* **219**:731-735, 1938.
19. Phemister, D. B., Rewbridge, A. G., and Rudisill, H., Jr. Calcium carbonate gall-stones and calcification of gall-bladder following cystic-duct obstruction. *Ann. Surg.* **94**:493-516, 1931.
20. Robins, S. A., and Hermanson, L. Cholangiography: modified technique for x-ray visualization of bile ducts during operation. *Surg., Gynec. & Obst.* **62**:684-688, 1936.
21. Saralegui, J. A. Cholangiography: new technique and results. *Am. J. Roentgenol.* **32**:167-170, 1934.

LABORATORY NOTE

A SIMPLE TECHNIC FOR RAPID SECTIONING

H. Edward MacMahon, M.D.,* and Shirley B. DelVecho†

CAMBRIDGE, MASSACHUSETTS

IN SELECTED cases the value of an immediate diagnosis at the operating table cannot be overemphasized. The methods of obtaining this information vary. The usual procedure is to freeze tissue, cut a section with a microtome, stain it by dipping in staining solution, rinse it in water and mount it in water or gelatin. There are many minor modifications of this, which is not to be wondered at since the preparation of such sections is still customarily carried out by the pathologist rather than by his technician, and since each pathologist has adopted his own way of handling, cutting and staining tissues. Yet all these technics appear to rely on a microtome, a sharp microtome knife, a tank of carbon dioxide, a bottle of staining solution, glass rods, picks, brushes, staining dishes, rinsing dishes, filter paper, funnels, slides, coverslips and towels. Added to this list, in the case of the peripatetic pathologist, is an assortment of wrenches, wooden blocks and washers, and last but not least a stout, reinforced bag for carrying this equipment.

The following method has been successfully tried over a period of a year, and because of its simplicity it has a particular application to the work of the pathologist in the field. The procedure is so quick and so accurate that it warrants a trial. If one wishes to carry out the usual freezing technic as well, no time is lost, for the method here described can be completed during the few seconds that elapse while the tissue is being frozen for sectioning. It is quite inexpensive, for it eliminates the microtome, microtome knife, carbon dioxide, staining solution and practically all the paraphernalia that have just been enumerated. The basis of this method is the staining of a thin layer of fresh, unfixed and unfrozen tissue, with a stain that, instead of being preserved as a liquid, is kept as a thin, dry film over the surface of an ordinary glass slide.

Some difficulty was encountered in obtaining thin, even films, but this has been overcome by coating one surface of the slide with Mayer's albumen-glycerin mixture, a space being left at one end of the slide for handling, and dipping it for a few seconds in the staining solution — a 1 per cent aqueous solution of toluidine blue. The slide is then drained, the reverse side is wiped free of stain, and to ensure a uniformly stained surface the slide is left on a flat surface until dry. Several slides can be prepared at one time and kept indefinitely, being always ready for use.

The only equipment required is a safety-razor blade, a prepared stained slide, a clean slide and a clean coverslip — all of which can be carried in a vest pocket. The technic is as follows:

Cut a thin section that can be easily handled.
Holding the section on the blade, gently place it on the ball of a finger.
Draw the stained slide lightly and quickly across the section, staining only one surface of the tissue.
Immerse the tissue in water.
Mount the tissue on a glass slide with the stained surface up.
Place a coverslip over the section, and with a good light examine the tissue.

The results of this technic have been as good as, if not better than, those obtained by the longer and more complicated procedures. It has been tried on breast tissue, lymph nodes, endometrial curettings, cervical tissue and fragments of rectal mucosa. During the trial period the accepted freezing method was used at the same time in each case, and as is the custom, permanent sections were ultimately prepared. In no case did the frozen-section or final report conflict with the original rapid-section diagnosis.

*Pathologist, Cambridge Hospital.
†Technician, Cambridge Hospital.

330 Mount Auburn Street

MEDICAL PROGRESS

ENDOCRINE ASPECTS OF CANCER (Concluded)*

IRA T. NATHANSON, M.D.†

BOSTON

CLINICAL OBSERVATIONS

Tumors of Breast

Carcinoma of breast. The peak of age incidence in 2165 cases of cancer of the breast at the onset was about forty-seven years.[122] The median age was fifty-two years, that is, as many cases occurred before that age as after it. Approximately a third of the patients were under forty-five years of age, another third from forty-five to fifty-five, and the remainder older than fifty-five. Taylor[123] found that about one third of the cases occurred during the period of mature ovarian function, another third appeared five years before and after the menopause and the remainder in women whose ovarian function had ceased five years or more. Thus, the two studies are in agreement but it must be pointed out that susceptibility to cancer of the breast steadily increases with age.[122] Further data on the relation of breast cancer to the menopause were supplied by Olch.[124] According to his studies 72 per cent of normal women pass through the menopause from forty to fifty years of age, whereas 55 per cent of those with cancer are still menstruating at the age of fifty. It was concluded that almost five times as many women with breast cancer had a delayed menopause as compared with normal women. Data on the length of the menopause are not readily available. This may be of importance for, even though amenorrhea is one of the primary signs of the climacteric, the ovary may continue to be active and secrete estrogens for a relatively long period.[125] Since corpus-luteum function is usually diminished or absent during the menopausal years, the normal cyclic change disappears and estrogen stimulation may continue unopposed. Cancer of the breast may appear many years after castration, even when the latter has been performed at an early age. Estrogens presumably of adrenal origin are still recovered from the urine of patients who have been castrated, as well as from the urine of postmenopausal women.[125] Herrell[126] reviewed the records of a large number of patients in the same age group with and without cancer of the breast. The findings disclosed that in the cancer group the incidence of complete ovariectomy before the tumor appeared was 1.5 per cent. The incidence in the noncancer group was 15.4 per cent, or ten times as great.

It is not known whether women who develop breast cancer have a higher percentage of menstrual disturbances than those who are free of the disease.[127] In one study, however, it was found that the menstrual pattern changed shortly before the discovery of the disease.[123] So far as can be determined there is no gross effect of the menstrual cycle on the primary tumor. The rapidity of growth of the primary tumor during pregnancy[128] and the appearance of a tumor in the second breast during another pregnancy,[129] which may ensue subsequent to treatment of the first lesion, is well recognized. Changes during lactation are usually more striking.[128] Whether these effects are caused by hormones elaborated in pregnancy or lactation or to the generalized metabolic changes has not been established.[130]

Breast disease in general is frequently associated with disease or abnormalities of the uterus and ovaries, and in this respect cancer of the breast is no exception.[123, 127] For example, Taylor[131] found that cancer of the breast and endometrium may arise in the same patient. This information suggests that the entire reproductive system may be subject to the same abnormal stimulus. Nulliparous women have a higher incidence of cancer of the breast than those who have borne children.[132] This appears to be the reverse of the situation in the mouse. Some believe that early weaning of the child or faulty lactation conduces to the development of breast cancer, in that they result in stasis and breakdown products which may cause chronic irritation.[133, 134] A study of 350 children of women with breast cancer revealed that 72 per cent were nursed for at least six months and of the remainder, a small number were deliberately weaned or not nursed because of inadequate milk supply.[123] Further studies of lactation are indicated, since there is a possibility of an abnormal physiologic state that in itself predisposes to cancer.

The significance of a relation between certain types of chronic cystic mastitis and cancer is a subject of much controversy. Warren's[135] studies, which were confirmed by Logie,[136] demonstrate that the attack rate of breast cancer for women with chronic cystic mastitis in the premenopausal group (thirty to forty-nine years of age) was nearly twelve times greater than that of the general female population in the same period. After the age of fifty it

*From the Medical Laboratories of the Collis P. Huntington Memorial Hospital, Harvard University, the Tumor Clinic of the Massachusetts General Hospital and the Pondville Hospital, Walpole, Massachusetts (Massachusetts Department of Public Health).

This is publication No. 598 of the Harvard Cancer Commission, Harvard University, and No. 106 of the Pondville Hospital.

†Instructor in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital; assistant surgeon, Pondville Hospital.

was two and five-tenths times as great, and for the entire group four and five-tenths times higher, suggesting that cancer may occur in association with or superimposed on the benign lesions during the period of greatest ovarian function.

Many have used castration as an adjunct to the treatment of cancer of the breast. This procedure is based on the work of Beatson,[137] who noted alleviation of signs and symptoms following castration in several women with cancer of the breast. Of late, x-ray therapy has usually been substituted for surgical extirpation of the ovaries.[138] The castration is of most value in premenopausal patients, although the effects are temporary, and seems to be of little benefit in the postmenopausal group. Bone metastases, as judged by x-ray examination, seem to regress partially or to disappear completely for a time. Relief from pain is frequently noted.[127] Effects on the primary tumor or lymph-node metastases are slight. It has been concluded that castration may be expected to result in temporary relief in about one third of the patients with extensive disease.[139] It cannot be demonstrated as definitely advantageous when employed as a prophylactic procedure in patients submitted to the radical operation. A report by Farrow and Adair[140] and an unpublished observation[141] revealed similar changes in the osseous metastases and in the relief of pain after orchidectomy in males with cancer of the breast. In many cases, laboratory evidence reveals discrepancies regarding the efficacy of x-ray castration as compared to surgical removal of the ovaries.[125] X-ray was adequate in some cases, as judged by the urinary estrogen excretion, but in others fluctuations in the output appeared even though the patients became amenorrheic. Hence, it is essential that, if castration by x-ray is to be used effectively, factors such as the age of the patient and the size of the portal are important in determining an adequate dosage.

Three reports have appeared on the possible development of cancer of the breast in women after prolonged administration with estrogens.[142–144] I know of at least 2 cases that have been associated with prolonged and intensive estrogen therapy. There is a good possibility that these were merely coincidental, but it certainly must be considered that the estrogens may have been contributory.

Attempts have been made to influence the course of cancer by the administration of hormones.[145] In our clinics, thus far, we have been unable to demonstrate a direct effect regarding augmentation or inhibition of the growth of the primary tumor by the injection of either estrogens or androgens. Farrow and Woodard[146] have noted that in the premenopausal group, skeletal metastases are apt to occur early. They also reported a marked acceleration of osseous metastases after intensive estrogen or androgen therapy. These changes were accompanied by an increased bone absorption and elevations in the serum and urinary calcium levels. Several cases in our clinics treated in a like fashion showed the same changes. In the past few years, however, reports have appeared concerning beneficial effects following prolonged androgen[147,148] and estrogen therapy[149, 150] in cancer of the breast. Many of the cases treated with the estrogenic hormone were given x-ray therapy in addition, and the effects of the latter were considered to be enhanced by the hormone treatment. These reports of a satisfactory response to hormone therapy are exceedingly difficult to evaluate at present, because in some cases factors such as complete histories and histologic confirmation of the disease are lacking. Until these methods of therapy receive further trial under carefully controlled conditions in large clinics, the subject must be left entirely open.

Excretion studies of the hormones with the present methods have failed to yield much information.[127] Several conclusions, however, may be drawn from such investigations: there is no significant deviation in the excretion of sex hormones in women with breast cancer: there is no proof that sex hormones are not involved in the disease or that abnormal secretion of the hormones does not accompany or precede the development of breast cancer — it is significant that normal excretion rates may be found in the presence of breast cancer; and cancer of the breast may be independent of hormonal influence once it develops.

The available evidence from all sources leads one to conclude that definite proof for the hormones as the direct cause of cancer is lacking. It is possible that in some cases they may be indirectly responsible by producing a fertile soil for the disease to develop.

Fibroadenoma of breast. These tumors seldom arise before puberty or after the menopause. Generally they are detected in the second and third decades. The lesions are usually slowly growing, and although they may pass unnoticed for a long time, it is possible that they arise in the early years after the menarche, when atypical menstrual activity is not infrequent. The disease is said to occur oftener in persons of a definite constitutional type, namely, nulliparous women with a relative underdevelopment of the pelvic organs and breasts.[123] The menstrual cycles are seldom abnormal when the patients are first seen, although some give a history of a period of abnormal cycles following the menarche.[127] Definite changes have been observed, however, in the size and the histologic appearance of the tumors during the menstrual cycle[151] and during pregnancy and lactation.[152, 153] Estrogens have been given over a long period to patients in the presence of and following the removal of fibroadenomas.[127] No new tumors have been observed that could be attributed to the hormone, since additional lesions frequently arise spontaneously. The significance of excretion studies of the sex hormones

are as yet equivocal.[127] Observations suggest that the origin of fibroadenomas may be explained partially on the basis of endocrine dysfunction. It is also possible that they arise as a result of atypical stimulation, especially since they usually occur when the metabolism and secretion of the sex hormones are at their height and may be abnormal.

Tumors of Uterus

Cancer of cervix. Cancers of the cervix arise more frequently in multiparous women than those who have not borne children. Hofbauer[154] advanced the theory that the increased incidence of cancer of the cervix in this group resulted from intensive hormone stimulation during pregnancy rather than from birth injuries. The median age of cancer of the cervix is about forty-nine years.[155] It is not infrequent to find the disease in women passing through the menopause, when the symptoms may be attributed to the climacteric syndrome. Cancer of the cervix is occasionally associated with cancer of the breast and myomas of the uterus but less so than is carcinoma of the endometrium.[156] In our clinics, 3 women have developed metaplasia of the cervical epithelium after estrogen administration. The lesions regressed after treatment was discontinued in two patients, but in the third case an early cancer was diagnosed, which was subsequently confirmed by hysterectomy. Other observers have reported the development of cervical cancer in 3 of 43 patients treated by estrogens for senile vaginitis.[157] Yet other investigators failed to find such lesions after treating over 200 women with estrogens over periods varying from a half to five and a half years.[158] Hence, at the present time, the relation of these cancers to the estrogenic hormone is equivocal. In a considerable number of cases, cervical polyps have developed after estrogen administration to postmenopausal women. Hormone excretion studies to date are few, and no conclusions can be drawn from them.[156]

Hyperplasia of endometrium. This lesion can be produced with comparative ease, especially in the absence of the ovaries in animals[62, 64, 89] and in women,[159] particularly after the menopause. It arises spontaneously at the menopause in patients in whom ovulation is apparently deficient and in the presence of granulosal-cell or thecal-cell tumors of the ovary. These tumors frequently give rise to elevated titers of estrogenic hormone in the urine. Most investigators are of the opinion that the lesion is caused by continuous stimulation by estrogens that is unopposed by hormones possessing a balancing effect, such as the corpus luteum.[156] These assumptions are based on studies on patients in whom persistent large unruptured follicles have been found in the absence of a recent corpus luteum.[160] The histologic changes vary from a proliferation of the endometrium to those simulating early adenocarcinoma.[156] The fact that these effects may be reversed by treatment with androgens and progesterone[161] or following castration by either radiation or surgery further incriminates estrogens as the initiating factor. According to Taylor,[156] the origin of cystic hyperplasia of the human endometrium as a result of unopposed stimulation with estrogens on the basis of ovarian dysfunction may be regarded as established. He further points out that the finding of endometrial hyperplasia in conjunction with a tumor of the reproductive tract is presumptive evidence that estrogens are of some significance in the origin of the neoplasm as well. Regarding endometrial hyperplasia arising in the years after the menopause, the explanation is more difficult. As already pointed out, the estrogenic hormone may be found in varying amounts in the urine long after the menopause. Excretion studies of urinary estrogenic hormone suggest an increased urinary output, but these need confirmation.[156]

Cancer of endometrium. This type of cancer is less frequent and usually occurs later in life than cancer of the cervix, suggesting that it may arise on a relatively senile endometrium. The median age in 331 cases was sixty-one.[155] According to statistical studies the disease is somewhat more frequent in nulliparous women and in those with a delayed menopause.[162] Several cancers of the endometrium have apparently arisen after long-continued administration of estrogens.[163] This may very well be coincidence since it seems likely that more cases would have come to attention considering the sensitivity of the endometrium to the hormone at any age. Nevertheless there are now a fair number of cases reported in which endometrial cancer has been found in association with granulosal-cell tumors of the ovary. Taylor[156] points out that, in view of the rarity of these ovarian tumors, it is hardly conceivable that the associated endometrial lesion was merely coincidence. He states, therefore, that in these particular cases it is difficult to deny the sequence of increased estrogen stimulation, hyperplasia of the senile endometrium and, finally, cancer. Since endometrial hyperplasia is part of the picture, it is of interest to investigate the significance of this lesion as a precancerous change. Endometrial hyperplasia is fairly frequent, but endometrial carcinoma is relatively rare, and although some believe that hyperplastic changes are a predisposing factor, long-term studies of these cases have shown that few patients eventually develop cancer.[156] Furthermore, even though cancer is sometimes found arising in association with endometrial hyperplasia, some are of the opinion that such an occurrence is purely accidental. This is discussed in some detail by Taylor.[156] It must be remembered, however, that as in the case of the relation of chronic cystic mastitis to cancer of the breast, agreement concerning the histologic criteria is of importance. Finally, it is of interest to point

out that cancer of the endometrium is oftener associated with cancer of the breast and fibromyomas of the uterus than is cancer of the cervix.[156, 164, 165] Hormone-excretion studies of significance in this disease have not been reported.

Fibromyomas. Many believe that fibromyomas of the uterus result from ovarian dysfunction. This is based particularly on the association of follicle cysts and endometrial hyperplasia with the disease, thereby suggesting excessive estrogenic stimulation,[166] but weighty evidence suggests that this is not the case. For example, Meyer[167] stressed that patients with fibroids become pregnant, menstruate normally and undergo typical cyclic changes, all of which is against ovarian dysfunction as a cause of the disease. It is well known that a certain number of lesions regress after the menopause or castration. This is far from constant and, as has been pointed out, may be related to the blood supply, especially since fibroids with adhesions to extrapelvic organs may continue to grow.[156] There are reports on the regression of fibroid tumors after treatment with testosterone and progesterone, but these are difficult to assess. A study of the excretion rates of the sex hormones in this disease failed to reveal any gross abnormalities.[168] Thus far the only convincing evidence for a hormonal etiology is the regression of the tumors after ovarian activity has ceased.

Tumors of Prostate Gland

Hypertrophy of prostate gland. Benign prostatic hypertrophy, that is, nodular hyperplasia, occurs in men over forty years of age. The disease increases with advancing age, so that between the ages of eighty and ninety, 75 per cent of men have some degree of nodular hyperplasia.[108] Obstructive symptoms, however, reach a maximum at about sixty-three years. As suggested by Moore,[108] this may mean that the etiologic agent becomes active after forty years of age, reaches its maximum soon after sixty and then decreases in intensity, but still remains capable of producing additional or new nodules. Some statistics indicate that benign hypertrophy is less frequent in single men.[169] Nodular hyperplasia of the prostate does not occur in the posterior lobe. Moszkowicz[170] showed that the structure of the prostate in the pseudohermaphrodite is dependent on the type of gonad present: the prostate is composed only of the middle and lateral lobes in the presence of ovaries, whereas in the presence of testes the entire prostate is found. These observations indicate that the posterior lobe is primarily a masculine organ, whereas the other lobes are ambisexual, that is, they can be stimulated by both estrogens and androgens.[108] There is no direct relation between the histologic appearance of the testes and benign prostatic hypertrophy. A survey of the literature by Moore[108] revealed, however, that, in a series of 28 eunuchs, eunuchoids and those with pituitary infantilism in whom the secondary sex characteristics were lost before the age of forty, there was not a single case of the disease, even though they all lived to be over forty-five years of age. The incidence would be quite high in a similar age group in the normal population. Hence, it appears that the disease does not develop in the absence of the testes.

The changes in the prostates of patients with testicular tumors are not consistent. Cases occur in children in whom signs of adrenal insufficiency are accompanied by those associated with adrenal hyperfunction, particularly the masculinizing syndrome. In these children there is a hyperplasia of the prostate gland similar to what occurs in adults with functioning adrenocortical tumors.[171] In primary Addison's disease the prostate does not differ from that in normal subjects.[108] Estrogens and androgens have been used in the treatment of benign prostatic hypertrophy, and although beneficial effects are said to occur, the consensus at present is that they are infrequently of any value.[172] Castration has also been reported as beneficial, but this too is controversial.[173] Excretion studies of the sex hormones suggest a decrease in androgens and estrogens in those patients as contrasted with the levels in normal men of the same age.[174, 175] Thus these observations, although not conclusive, suggest an endocrine dysfunction as a possible etiologic factor in the disease.

Cancer of prostate. The median age at the onset in 235 cases with cancer of the prostate was sixty-five.[155] It is rare below the age of thirty and increases steadily with advancing age. In fact in the eighth decade of life it is one of the most frequent of all carcinomas.[176] Prostatic cancer is rare in the Chinese[177] and has not been recorded in eunuchs or eunuchoids.[108] Routine autopsy studies of the prostate in man reveal an incidence of 10 to 15 per cent of latent carcinoma.[178–180] On one series of unselected consecutive autopsies on 50 men over fifty years of age, however, the prostate was examined by serial section and the incidence of occult carcinoma was 46 per cent, although prostatic carcinoma was not the cause of death in any case.[180]

Following the progress report of Quinby[181] in 1942 more material has accumulated, and it may be of interest to bring this up to date. Although castration was previously suggested and occasionally used as a treatment for cancer of the prostate, it was not until the excellent work of Huggins and his group[109, 110] on the effect of the hormones on the prostate and that of the Gutmans[182] on acid phosphatase that investigation of the hormonal relation to the disease received a real stimulus. The prostate in childhood contains small amounts of acid phosphatase, but the level rises considerably after puberty.[183] This enzyme, which is present apparently in large amounts only in the prostate,

seems to be directly related to the secretory activity of the gland.[184] Serum-acid phosphatase levels are frequently elevated in patients with cancer of the prostate, particularly those with bone metastases.[182, 185–187] Serum-alkaline phosphatase levels are also above normal in many cases in which osseous metastases are part of the clinical picture.[182] Excessive acid phosphatase can be demonstrated by histologic examination of neoplastic prostatic tissue.[188] Dean, Woodard and Twombly[189] state that patients may be placed in four groups, based on the serum-phosphatase levels:

> Normal men in whom there is no increase in either the serum acid or alkaline phosphatases. It is noteworthy that since every adult prostate contains large quantities of acid phosphatase and that the serum acid phosphatase of men is the same as that of women, who have no organ rich in acid phosphatase, this substance is prevented from entering the circulation by an intact prostatic capsule.
>
> Patients with cancers of the prostate and normal amounts of serum acid and alkaline phosphatase. In this small but definite group one may operate with an excellent chance of removing all of the disease because the tumor probably has not grown beyond the gland.
>
> A group consisting of the great majority of patients with prostatic carcinoma. The tumor has grown through the gland capsule and there may or may not be distant metastases. In our experience 73 per cent of these patients show increased serum acid phosphatase.
>
> Patients with prostatic cancers which metastasize to bones. There is nearly always an increase in the serum alkaline phosphatase in these cases. The quantity of this substance in the serum so accurately represents the amount of reaction of the bones to the invasion of prostatic carcinoma that quantitative assays give clinical information not obtained by any other tests, such as the roentgen rays.

Castration and injection of estrogens produce little change in the acid phosphatase level if it is normal before such therapy.[189] Castration and injection of estrogens, however, into patients with prostatic cancer having marked elevation of the acid phosphatase result in a sharp reduction of the levels of the enzyme, but seldom to normal.[190] Administration of androgens produces a sharp rise in the serum acid phosphatase.[190] Alkaline phosphatase following castration or injection of estrogens into patients with metastatic disease may rise, show no change or decrease, either at once or after a latent period.[189] These observations have been of inestimable value in the diagnosis of the extent and recurrence of the disease.

Castration or the administration of estrogens, or both, produce apparent regressions of the prostatic lesions and their metastases in many patients.[188, 189, 191–193] Serial biopsies of the tumor reveal marked degenerative changes in the cells when stilbestrol is given over a fairly long period of time.[194] Administration of androgens seems to increase the activity of the process.[190, 193]

Excretion studies of the sex hormones in the untreated case before and after castration or hormone administration are of interest. Following castration a decreased estrogen excretion has been reported, whereas the 17-ketosteroids (androgens) after a slight initial fall may rise above the pretreatment level.[189, 195, 196] Pituitary gonadotropin increases in the urine following castration, as is the case in menopausal or castrated women or in men who have undergone the climacteric. Injection of estrogens may decrease the 17-ketosteroids and pituitary gonadotropic levels in the urine, and the urinary estrogen titers may rise.[189] Thus it appears that the mechanism by which these two methods produce their similar beneficial effect may be somewhat different. The primary effect in the case of estrogen therapy seems to be on the tropic functions of the anterior pituitary gland, which are inhibited and in turn result in decreased stimulation of the organs that may produce androgens (gonads and adrenal glands). Castration, although removing one source of androgens, allows for increased pituitary activity, which may stimulate other organs, such as the adrenal glands, to increased androgen production.

Concerning the therapeutic value and marked clinical improvement following castration or estrogen administration, or both, there can be no doubt. It is still unsettled which form of therapy is the best. Castration or estrogens alone or in combination either simultaneously or successively all have their adherents. The greatest hopes for the treatment, however, have not materialized. Certain cases do not respond to treatment at all, whereas others show striking clinical improvement and relief from pain. This may be related to the histologic type of tumor, since those lesions that more nearly resemble the adult gland seem to respond best to the therapy.[193] It has also been conceded that the treatment in itself cannot be considered a curative procedure but should be reserved for palliative purposes. To date, there is no substitute for radical surgical procedures in operable cancer of the prostate without metastases. On the basis of present evidence, castration or hormone therapy should not be resorted to as the primary treatment in this type of case. Most patients who benefit from castration or estrogen therapy have recurrence of the signs and symptoms within a few years and many are not relieved for more than a few months.[189, 193, 197] Some patients live without symptoms or obvious signs of activity of the disease for long periods of time, but as yet there is no definite evidence of true curability. It must be remembered that cancer of the prostate varies in its course and degree of malignancy so that the untreated patient or those receiving palliative surgical measures may live for a long time without benefit of any other form of therapy.[155] The final answer must await longer periods of observation.

Tumors of Testis

Tumors of the testicle are essentially diseases of the young. Approximately 75 per cent of the lesions arise in patients under the age of forty, and the average age incidence is about thirty-five.[155, 198]

In other words, these tumors appear at a time when the male is most active sexually. This age incidence is distinctly different from that of most other types of malignant neoplasm and suggests causation by other agents. It is also well recognized that tumors of the testicle occur more frequently in men with undescended testes. Gilbert and Hamilton[199] found that in 345 of 835 reported cases of teratoma of the testicle the lesions were intra-abdominal. Eleven per cent of the 345 occurred in pseudohermaphrodites. This does not mean that when unilateral cryptorchidism is present the tumors always appear in the undescended testis. In one study it was found that the tumor occurred in the normal gonad in 23 of 744 patients with unilateral cryptorchidism,[199] and in another series the incidence was 6 in 27 cases.[198] These findings, however, suggest a possible hormonal factor.

Excretion studies of the hormones are of great interest in tumors of the testicle. Gonadotropic substances are often excreted in increased amounts in the urine of patients with testicular tumors.[200] Two types have been identified — one similar to the chorionic gonadotropin normally found in the urine of pregnant women,[201] and the other a gonadotropin similar to that found in human beings who have been castrated or who have passed through the menopause.[202] The latter will be referred to as the pituitary type of gonadotropin. Some malignant tumors of the testes, although histologically similar to those resulting in increased secretion of gonadotropins, fail to show any increase; clinically such cases behave identically with those in which the hormone titer is elevated.[198,202] Furthermore, as pointed out by Hamburger[202] and by Twombly,[198] the pituitary type of gonadotropin may be present in increased quantities in the urine in the absence of active tumors. It does not vary with treatment or progression of the disease. Although it was formerly thought that the amount of hormone excreted paralleled the degree of malignancy of the tumor, it has recently been shown that this cannot be relied on to be pathognomonic of cell type, any more than can the nature of the hormone excreted.[203] In general, however, chorionic gonadotropin is likelier to be associated with embryonal adenocarcinomas and chorioepitheliomas, whereas elevations of the pituitary type of hormone usually accompany seminomas, there being exceptions in both groups. Both hormones are often found in the same patient, which suggests that many testicular tumors consist of mixed cell types.[198, 204, 205]

These hormone studies are of interest in prognosis. It has been stated that cases showing unusually large amounts of the hormones in the urine have a poor prognosis. Hamburger, Bang, and Nielsen[204] based their observations, however, on differentiation of the two forms of hormones excreted. They are of the opinion that the chorionic type is secreted by the tumor, since this hormone is biologically similar to that secreted by the normal placenta. Moreover, there appears to be a close correlation between the amount excreted and the extent of the neoplastic disease. Twombly[198] states that this type of hormone in male urine does not appear except when tumor is proved to be present. Several observers agree that the chorionic gonadotropin is likely to be indicative of a radioresistant type of tumor, whereas tumors associated with an increased excretion of the pituitary type of gonadotropin are usually radiosensitive.[204] Excretion studies are also of value in studying the course of the disease. If there are no metastases and the tumor is secreting large amounts of hormones, orchidectomy will usually be followed by a prompt disappearance of the hormones. If metastases appear subsequently, the hormone levels may again rise, and in some cases may predict recurrences before they can be detected clinically. If metastases are present at the time of orchidectomy the titer may show little change. The effectiveness of x-ray therapy in the metastatic lesions in some cases may also be determined by a study of the excretion rates.

Abnormal estrogen excretion may be found in the presence of these tumors, particularly those that produce large amounts of chorionic gonadotropin.[198] Pregnanediol, the excretion product of the corpus luteum hormone, was also found to be elevated in one case of chorioepithelioma.[198]

The excretion of biologically active androgens is definitely decreased in a high percentage of seminomas.[206] In cases showing chorionic gonadotropin, levels below normal were found in about half the cases studied. Hamburger and Godtfredsen[206] believe that the formation of chorionic gonadotropin may stimulate the remaining testis and the adrenal glands, causing the production of male hormone. This might explain the difference in the findings between these two types of tumors.

Attempts to influence the course of testicular tumors by hormones have been made by Twombly.[198] Administration of antigonadotropic principles resulted in the increase of the hormone titers. Estrogens were also tried on 2 patients without any striking change. Saleeby[207] suggested that bilateral gonadectomy should be done and cites a case in which the patient seemed to improve after the procedure was carried out. Evaluation is complicated, however, by the fact that the patient had x-ray therapy as well.

Significance of Hormone Excretion

Urinary excretion levels of the sex hormones represent only the end product of metabolism. It is not definitely known whether they give true indices of the blood levels, the rate of secretion or destruction and the utilization of the hormones by the tissues. Furthermore, they do not reveal the exact nature or relation of the various components of the hormones excreted. Thus far, the study of

hormone excretion is of the greatest value in patients who have functioning tumors of the adrenal glands and the gonads, such as adrenocortical hyperplasias, adenomas and carcinomas, granulosal-cell and thecal-cell tumors of the ovary, arrhenoblastomas, and teratoid tumors and interstitial-cell tumors of the testes. The excretion rates in these cases are of inestimable help in making the diagnosis and in following the course of the disease. Recent studies on the isolation of the sex hormones suggest that patients with cancer may excrete estrogens and 17-ketosteroids in a different fashion from persons without cancer. The usual relation of the individual components of both the estrogens[208] and 17-ketosteroids[209, 210], may be atypical as well as the ratio between the total estrogenic and 17-ketosteroid complexes. It is clear that alterations in excretion levels or in the specific type of hormone excreted are not necessarily characteristic for patients with cancer. They may merely represent deviations from normal that occur only as a result of disturbed metabolism in the sick person. They indicate, however, a distinct abnormality, and as such are significant in the study of the disease.

Conclusions

A considerable number of data bearing on the relation of the endocrine organs to tumors have accumulated. The administration of sex hormones to experimental animals has resulted in the production, the augmentation and the inhibition of benign and malignant tumors. These changes are limited to definite types of tumors in different species, as well as to certain strains in any one species of animal. Thus, there are other factors that determine the reaction of a tumor to a hormonal stimulus, and the susceptibility of an animal to the induction of a neoplasm. It is difficult to interpret these facts in terms of human cancer. Nevertheless, they are of extreme importance in the study of the origin and course of cancer in general.

Strong evidence exists to indicate that endocrine factors are associated with some human tumors. There is as yet no conclusive proof that these influences are directly concerned with cancer, although an increasing number of cases are coming to light in which cancer developed after intensive estrogen therapy in organs such as the uterus and breast, which are normally stimulated by these hormones. It is probable that this is coincidence, but the association cannot be ignored. Present evidence suggests that the sex hormones are not in themselves carcinogenic. It is likelier that, as a result of excessive stimulation or atypical metabolism, the tissues of susceptible persons are conditioned to the action of a carcinogenic agent.

There is little to support the therapeutic value of hormones in the treatment of any cancer except that of prostatic origin. Judgment must be reserved until much more information is obtained regarding the treatment of cancer of the breast or other organs with either estrogens or androgens. There is no question that castration as an adjunct to the treatment of selected cases of cancer of the breast and prostate and the administration of estrogens to patients with cancer of the prostate have been of great benefit. Such treatment should be reserved for palliative purposes only, since there is at present no substitute for established methods of surgery and radiation in the operable patient. Indiscriminate use of the sex hormones may also produce untoward effects in other ways. It therefore behooves all to be extremely cautious in the use of the sex hormones for any syndrome, even when the indication for treatment is well defined.

References

122. Nathanson, I. T., and Welch, C. E. Life expectancy and incidence of malignant disease. I. Carcinoma of breast. *Am. J. Cancer* **28**:40-53, 1936.
123. Taylor, H. C., Jr. Evidence for endocrine factor in etiology of mammary tumors. *Am. J. Cancer* **27**:525-541, 1936.
124. Olch, I. Y. Menopausal age in women with cancer of breast. *Am. J. Cancer* **30**:563-566, 1937.
125. Nathanson, I. T., Rice, C., and Meigs, J. V. Hormonal studies in artificial menopause produced by roentgen rays. *Am. J. Obst. & Gynec.* **40**:936-945, 1940.
126. Herrell, W. E. Relative incidence of oophorectomy in women with and without carcinoma of breast. *Am. J. Cancer* **29**:659-665, 1937.
127. Nathanson, I. T. Relationship of hormones to diseases of breast. *Surgery* **16**:108-140, 1944.
128. Smith, F. R. Effect of pregnancy on malignant tumors. *Am. J. Obst. & Gynec.* **34**:616-633, 1937.
129. Trout, H. H. Remaining breast after radical removal of opposite side for carcinoma. *Surg., Gynec. & Obst.* **34**:630-632, 1922.
130. Taylor, G. W., and Meltzer, A. "Inflammatory carcinoma" of breast. *Am. J. Cancer* **33**:33-49, 1938.
131. Taylor, H. C., Jr. Coincidence of primary breast and uterine cancer. *Am. J. Cancer* **15**:277-279, 1931.
132. Lane-Claypon, C. E. *Further Report on Cancer of the Breast with Special Reference to Its Associated Antecedent Conditions.* Report on Public Health and Medical Subjects, No. 32, London: Great Britain Ministry of Health, 1936.
133. MacDonald, I. Mammary carcinoma: review of 2,636 cases. *Surg., Gynec. & Obst.* **74**:75-82, 1942.
134. Adair, F. E. Etiological factors of mammary cancer in 200 women: also control study of 100 normal American women. *New York State J. Med.* **34**:61-68, 1934.
135. Warren, S. Relation of "chronic mastitis" to carcinoma of breast. *Surg., Gynec. & Obst.* **71**:257-273, 1940.
136. Logie, J. W. Mastopathia cystica and mammary carcinoma. *Cancer Research* **2**:394-397, 1942.
137. Beatson, G. T. On treatment of inoperable cases of carcinoma of mamma: suggestions for new method of treatment with illustrative cases. *Lancet* **2**:104-107 and 162-165, 1896.
138. Ahlbom, H. Castration by roentgen rays as auxiliary treatment in the radiotherapy of cancer mammae at Radiumhemmet, Stockholm. *Acta radiol.* **11**:614-635, 1930.
139. Taylor, G. W. Evaluation of ovarian sterilization for breast cancer. *Surg., Gynec. & Obst.* **68**:452-456, 1939.
140. Farrow, J. H., and Adair, F. E. Effect of orchidectomy on skeletal metastases from cancer of male breast. *Science* **95**:654, 1942.
141. Nathanson, I. T. Unpublished data.
142. Allaben, G. R., and Owen, S. E. Adenocarcinoma of breast coincident with strenuous endocrine therapy. *J. A. M. A.* **112**:1933, 1939.
143. Auchincloss, H., and Haagensen, C. D. Cancer of breast possibly induced by estrogenic substance. *J. A. M. A.* **114**:1517-1523, 1940.
144. Parsons, W. H., and McCall, E. F. Role of estrogenic substances in production of malignant mammary lesions, with report of case of adenocarcinoma of breast, possibly induced by strenuous estrogen therapy. *Surgery* **9**:780-786, 1941.
145. Farrow, J. H. Effect of sex hormones on skeletal metastases from breast cancer. *Surgery* **16**:141-151, 1944.
146. Farrow, J. H., and Woodard, H. Q. Influence of androgenic and estrogenic substances on serum calcium in cases of skeletal metastases from mammary cancer. *J. A. M. A.* **118**:339-343, 1942.
147. Loeser, A. A. Mammary carcinoma: response to implantation of male hormone and progesterone. *Lancet* **2**:698-700, 1941.
148. Fels, E. Treatment of breast cancer with testosterone propionate. *J. Clin. Endocrinol.* **4**:121-125, 1944.
149. Binnie, G. G. Regression of tumours following treatment by stilboestrol and x-ray therapy, with notes on case of breast tumour which regressed with stilboestrol alone. *Brit. J. Radiol.* **17**:42-45, 1944.
150. Foreign letter (London). Diethylstilbestrol in cancer of breast. *J. A. M. A.* **125**:1203, 1944.
151. Ingleby, H. Relation of fibro-adenoma and chronic mastitis to sexual cycle changes in breast. *Arch. Path.* **14**:21-41, 1932.
152. Kilgore, A. R. Tumors and tumor-like lesions of breast in association with pregnancy and lactation. *Arch. Surg.* **18**:2079-2098, 1929.
153. Geschickter, C. F., and Lewis, D. Pregnancy and lactation changes in fibro-adenoma of breast. *Brit. M. J.* **1**:499-504, 1938.
154. Hofbauer, J. Graviditätsveränderungen des Cervixepithels und ihre Stellung in der Ätiologie des Uteruskarzinoms. *Zentralbl. f. Gynäk.* **55**:428-435, 1931.

155. Welch, C. E., and Nathanson, I. T. Life expectancy and incidence of malignant disease. IV. Carcinoma of genito-urinary tract. *Am. J. Cancer* **31**:586-597, 1937.
156. Taylor, H. C. Jr. Endocrine factors in origin of tumors of uterus. *Surgery* **16**:91-107, 1944.
157. Gemmell, A. A., and Jeffcoate, T. N. A. Oestrogens and carcinoma of uterus. *J. Obst. & Gynaec. Brit. Emp.* **46**:985-993, 1939.
158. Geist, S. H., and Salmon, U. J. Are estrogens carcinogenic in human female? Effect of long-continued estrogen administration upon uterine and vaginal mucosa of human female. *Am. J. Obst. & Gynec.* **41**:29-36, 1941.
159. Zondek, B. Effect of prolonged administration of estrogen on uterus and anterior pituitary of human beings. *J. A. M. A.* **114**:1850-1854, 1940.
160. Schröder, R. Anatomische Studien zur normalen und pathologischen Physiologie des Menstruationszyklus. *Arch. f. Gynäk.* **104**:27-102, 1915.
161. Seegar, G. E. Histologic effect of progesterone on hyperplastic endometria. *Am. J. Obst. & Gynec.* **39**:469-476, 1940.
162. Crossen, R. J., and Hobbs, J. E. Relationship of late menstruation to carcinoma of the corpus uteri. *J. Missouri M. A.* **32**:361-363, 1935.
163. Meigs, J. V. Personal communication.
164. Bowers, D. D. Cancer and fibromyomas of uterus. *Am. J. Obst. & Gynec.* **39**:830-836, 1940.
165. Oesterlin, E. J., and Cron, R. S. Coexistence of uterine myoma and fundal carcinoma. *Am. J. Obst. & Gynec.* **29**:176-181, 1935.
166. Witherspoon, J. T. Interrelationship between ovarian follicle cysts, hyperplasia of endometrium and fibromyomata: possible etiology of uterine fibroids. *Surg., Gynec. & Obst.* **56**:1026-1035, 1933.
167. Meyer, R. Die Pathologie der Bindegewebsgeschwülste und Mischgeschwülste. In Stoeckel. *Handbuch der Gynäkologie*. Munchen: J. F. Bergmann. 1930. P. 211.
168. Furuhjelm, M. On excretion of oestrogenic and androgenic substances in urine of women: investigation covering 14 healthy women, 10 cases of myoma and 2 of castration. *Acta obst. et gynec. Scandinav.* (Supp. I) **20**:1-91, 1940.
169. Gover, M. Statistical study of etiology of benign hypertrophy of prostate gland. *Johns Hopkins Hosp. Rep.* **21**:231-295, 1923.
170. Moszkowicz, L. Die Prostata der Zwitter und die Systematik des Zwittertums. *Virchows Arch. f. path. Anat.* **295**:211-235, 1935.
171. Dijkhuizen, R. K., and Behr, E. Adrenal hypertrophy in infants. New clinical entity of neonatal period. *Acta paediat.* **27**:279-295, 1939.
172. Heckel, N. J. Evaluation of sex hormones in treatment of benign prostatic hypertrophy, carcinoma of prostate and other diseases of genitourinary system. *J. Clin. Endocrinol.* **4**:166-172, 1944.
173. Huggins, C., and Stevens, R. A. Effect of castration on benign hypertrophy of prostate in man. *J. Urol.* **43**:705-714, 1940.
174. Dingemanse, E., and Laqueur, E. Content of male and female hormone in urine of patients with prostatic hypertrophy. *J. Urol.* **44**:530-540, 1940.
175. Moore, R. A., Miller, M. L., and McLellan, A. Urinary excretion of androgens by patients with benign hypertrophy of prostate. *J. Urol.* **44**:727-737, 1940.
176. Duff, J. Cancer mortality, bladder, kidney, and prostate, 1917 to 1928. *J. Urol.* **32**:346-353, 1934.
177. Hu, C. H., and Ch'in, K. Y. Statistical study of 2,179 tumors occurring in Chinese. *Chinese M. J.* **1**:43-63, 1936.
178. Rich, A. R. On frequency of occurrence of occult carcinoma of prostate. *J. Urol.* **33**:215-233, 1935.
179. Moore, R. A. Morphology of small prostatic carcinoma. *J. Urol.* **33**:224-234, 1935.
180. Baron, E., and Angrist, A. Incidence of occult adenocarcinoma of prostate after fifty years of age. *Arch. Path.* **32**:787-793, 1941.
181. Quinby, W. C. Carcinoma of prostate. *New Eng. J. Med.* **227**: 512-515, 1942.
182. Gutman, A. B., and Gutman, E. B. "Acid" phosphatase occurring in serum of patients with metastasizing carcinoma of prostate gland. *J. Clin. Investigation* **17**:473-478, 1938.
183. Gutman, A. B., and Gutman, E. B. "Acid" phosphatase and functional activity of prostate (man) and preputial glands (rat). *Proc. Soc. Exper. Biol. & Med.* **39**:529-532, 1938.
184. Gomori, G. Distribution of acid phosphatase in tissues under normal and under pathologic conditions. *Arch. Path.* **32**:189-199, 1941.
185. Robinson, J. N., Gutman, E. B., and Gutman, A. B. Clinical significance of increased serum "acid" phosphatase in patients with bone metastases secondary to prostatic carcinoma. *J. Urol.* **42**: 602-617, 1939.
186. Sullivan, T. J., Gutman, E. B., and Gutman, A. B. Theory and application of serum "acid" phosphatase determination in metastasizing prostatic carcinoma: early effects of castration. *J. Urol.* **48**:426-458, 1942.
187. Herger, C. C., and Sauer, H. R. Relationship of serum acid phosphatase determination to presence of bone metastases from carcinoma of prostate. *J. Urol.* **46**:286-302, 1941.
188. Huggins, C., Stevens, R. E., Jr., and Hodges, C. V. Studies on prostatic cancer. II. Effects of castration on advanced carcinoma of prostate gland. *Arch. Surg.* **43**:209-233, 1941.
189. Dean, A. L., Woodard, H. Q., and Twombly, G. H. Endocrine treatment of cancers of prostate gland. *Surgery* **16**:169-180, 1944.
190. Huggins, C., and Hodges, C. V. Studies on prostatic cancer. I. Effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of prostate. *Cancer Research* **1**:293-297, 1941.
191. Randall, A. Eight-year results of castration for cancer of prostate. *J. Urol.* **48**:706-709, 1942.
192. Chute, R., Willets, A. T., and Gens, J. P. Experiences in treatment of carcinoma of prostate with stilbestrol and with castration by technique of intra-capsular orchidectomy. *J. Urol.* **48**:682-692, 1942.
193. Huggins, C. Effect of orchiectomy and irradiation on cancer of prostate. *Ann. Surg.* **115**:1192-1200, 1942.
194. Schenken, J. R., Burns, E. L., and Kahle, P. J. Effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of prostate gland. II. Cytologic changes following treatment. *J. Urol.* **48**:99-112, 1942.
195. Scott, W. W., and Vermeulen, C. Studies on prostatic cancer. V. Excretion of 17-ketosteroids, estrogens and gonadotropins before and after castration. *J. Clin. Endocrinol.* **2**:450-456, 1942.
196. Satterthwaite, R. W., Hill, J. H., and Packard, E. F. Experimental and clinical evidence on role of 17-ketosteroids in prostatic carcinoma. *J. Urol.* **46**:1149-1153, 1941.
197. Smith, G. G. Personal communication.
198. Twombly, G. H. Relationship of hormones to testicular tumors. *Surgery* **16**:181-193, 1944.
199. Gilbert, J. B., and Hamilton, J. B. Studies in malignant testis tumors. III. Incidence and nature of tumors in ectopic testes. *Surg., Gynec. & Obst.* **71**:731-743, 1940.
200. Ferguson, R. S. Quantitative behavior of prolan A in teratoma testis. *Am. J. Cancer* **18**:269-295, 1933.
201. Fevold, H. L., Fiske, V. M., and Nathanson, I. T. Physiological reactions produced by gonadotropic hormone from urine of case of chorio-epithelioma. *Endocrinology* **24**:578-580, 1939.
202. Hamburger, C. On nature of gonadotrophin in cases of malignant tumors of testis. *Acta. path. et microbiol. Scandinav.* **18**:457-484, 1941.
203. Twombly, G. H., Temple, H. M., and Dean, A. L. Clinical value of Aschheim-Zondek test in diagnosis of testicular tumors. *J. A. M. A.* **118**:106-111, 1942.
204. Hamburger, C., Bang, F., and Nielsen, J. Studies on gonadotropic hormones in cases of testicular tumors (attempt at classification of testicular tumors on basis of their hormonal, histological and clinico-radiological properties). *Acta path. et microbiol. Scandinav.* **13**: 75-102, 1936.
205. Furuhjelm, L. Excretion of gonadotropic hormones in urine of cases of tumor of testis. *Nord. med.* **11**:2603-2609, 1941.
206. Hamburger, C., and Godtfredsen, E. Studies on excretion of androgenic substances and gonadotrophin in cases of malignant tumors of testis, especially seminoma. *Acta path. et microbiol. Scandinav.* **18**:485-502, 1941.
207. Saleeby, E. R. Teratoma of testicle: metastases to epigastrium treated by bilateral orchidectomy — recovery. *Ann. Surg.* **119**: 262-265, 1944.
208. Pincus, G., and Pearlman, W. H. Steroid excretion in cancerous and noncancerous persons: urinary estrogens. *Cancer Research* **1**: 970-974, 1941.
209. Pearlman, W. H. Steroid excretion in cancerous and non-cancerous persons: 17-ketosteroids. *Endocrinology* **30**:270-276, 1942.
210. Dobriner, K., Rhoads, C. P., Lieberman, S., Hill, B. R., and Fieser, L. F. Abnormal alpha ketosteroid excretion in patients with neoplastic disease. *Science* **99**:494-496, 1944.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
BENJAMIN CASTLEMAN, M.D., *Acting Editor*
EDITH E. PARRIS, *Assistant Editor*

CASE 30501

PRESENTATION OF CASE

First admission. A forty-nine-year-old electrician was admitted to the hospital with substernal pain of twenty-four hours' duration.

The patient was well until the day before admission, when he suddenly developed a sensation of breathlessness and a lump in his throat. This lasted a few moments and was followed an hour later by a squeezing sensation beneath the sternum, with pain radiating to the deltoid region and down the extensor surface of the right arm. This was accompanied by nausea and a recurrence of the feeling of breathlessness. A physician gave him "an injection and some pills." He vomited eight times during the night. On the morning of admission the pain appeared to be epigastric, radiating to the top of the sternum. For five years prior to admission the patient had had attacks of "indigestion" associated with pain radiating to the head and with spots before the eyes.

Physical examination revealed a well-developed and well-nourished, restless man complaining of substernal pain. The skin was dry, and the heart, lungs and abdomen were normal.

The temperature was 100°F., the pulse 68, and the respirations 16. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 5,000,000, with 17.5 gm. of hemoglobin, and a white-cell count of 15,000, with 80 per cent neutrophils. The urine and stools were normal. The erythrocytic sedimentation rate was 24 mm. per hour, total fall (0.8 mm. per minute, corrected). The serum cholesterol was 292 mg. per 100 cc.

An electrocardiogram taken on admission revealed an ST takeoff slightly elevated in Lead 1 and markedly elevated in Lead 4. T_1 and T_4 were inverted, R_4 was absent, and ST_4 was slurred.

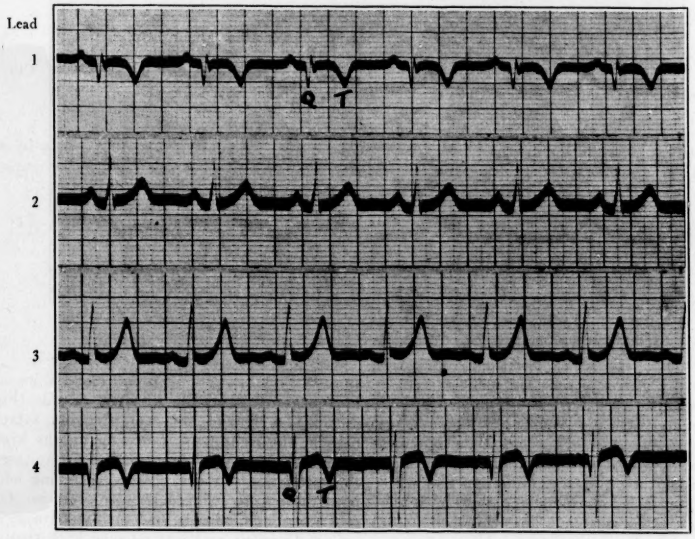

FIGURE 1. *Electrocardiogram during the Acute Anterior Myocardial Infarction in 1942.*

The patient was treated with morphine and bed rest and quickly became asymptomatic. The temperature fell to normal on the fifth hospital day, and the white-cell count gradually fell to 7600 over a period of about two weeks. The corrected sedimentation rate gradually fell to 0.6 mm. per minute. A subsequent electrocardiogram (Fig. 1) showed

*On leave of absence.

changes characteristic of involution of a large anterior-wall infarction with prominent Q waves and inverted T waves in Leads 1 and 4. He was discharged on the forty-second hospital day.

Second admission (eight months later). Following discharge the patient was followed in the Out-Patient Department, where he showed progressive improvement. He continued to have slight precordial pain, however, with mild choking sensations and dyspnea.

Two nights before his second admission, after a day of unusual exertion, he suddenly developed severe substernal pain radiating down both arms

version of the T waves in Leads 1 and CF_4. A subsequent tracing (Fig. 3) showed a return to normal rhythm, and the remaining changes were considered characteristic of the evolution of a posterior-wall infarction. The temperature and white-cell count rapidly returned to normal. He was discharged on the thirty-fifth hospital day.

Final admission (one year later). Following discharge the patient was unable to work and remained at home. An electrocardiogram two months after discharge (Fig. 4) showed normal rhythm at a rate of 100, with small Q waves and low T waves in Leads 1, 2 and 3 and fairly normal tracings in

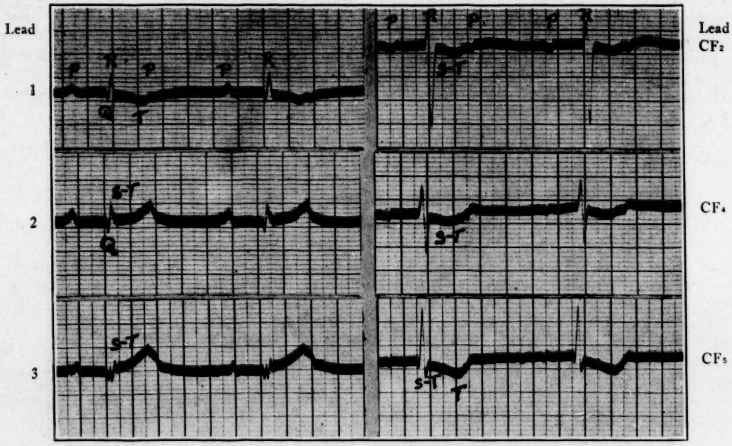

FIGURE 2. *Electrocardiogram during the Acute Posterior Myocardial Infarction in 1943.*

and relieved by nitroglycerin. He spent a restless night in moderate discomfort and remained in bed the following day. On the evening before admission a similar but severer attack occurred, which was accompanied by a sense of suffocation.

On admission the physical examination was negative except for an inconstant gallop rhythm at the apex, thought to be systolic. The white-cell count was 19,600, with 89 per cent neutrophils.

On admission, the temperature was 96.4°F., rapidly rising to 102°, the pulse 54, rising to 100, and the respirations 20. The blood pressure was 160 systolic, 100 diastolic.

An electrocardiogram (Fig. 2) showed 2:1 auriculoventricular block, with a ventricular rate (R) of 50 and an auricular rate (P) of 100. Q_3 and Q_2 were small. There was depression of the ST segments in the precordial leads (CF_2, CF_4 and CF_5), with elevation in Leads 2 and 3. There was late in-

Leads CF_3, CF_4 and CF_5; it was much more normal in appearance than the previous records (Figs. 1, 2 and 3). He had, however, frequent attacks of pain in the right wrist radiating up the arm and across the upper chest, usually precipitated by slight exertion but occasionally occurring while at rest; these were relieved by nitroglycerin. On the day before admission he had such an attack; it was extremely severe and was relieved by nitroglycerin only for brief periods. Several hypodermic injections gave no relief. He also noted a dull pain over the lower right chest anteriorly. He felt weak and was dyspneic. During the night the pain in the arms and chest continued. He developed a dry hacking cough, was nauseated and perspired freely. He was admitted to the hospital the following morning.

Physical examination revealed an acutely ill, cyanotic man with warm, moist skin and rapid,

labored respirations. The heart sounds were distant and a Grade 2 blowing systolic murmur was present at the apex. There was slight dullness on the right side of the chest, with increase in the

The temperature was 100.4°F., the pulse 96, and the respirations 30. The blood pressure was 110 systolic, 75 diastolic.

Examination of the blood showed a white-cell

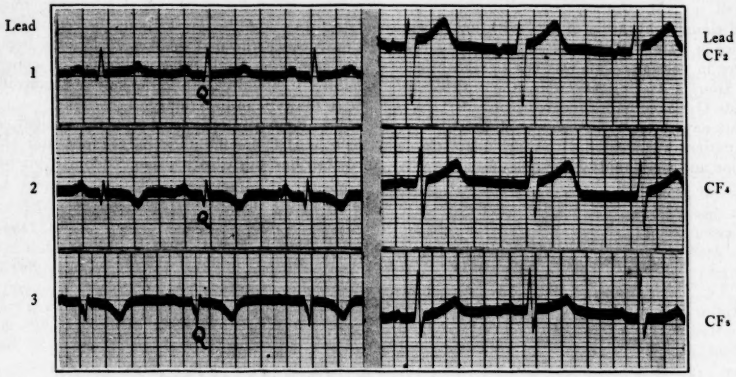

FIGURE 3. *Electrocardiogram Taken Three Weeks after That in Figure 2 and Showing Normal Precordial Leads.*

whispered voice. Numerous medium moist rales were present at both lung bases and at the right

count of 23,700, with 92 per cent neutrophils. The serum nonprotein nitrogen was 57 mg. per 100 cc.,

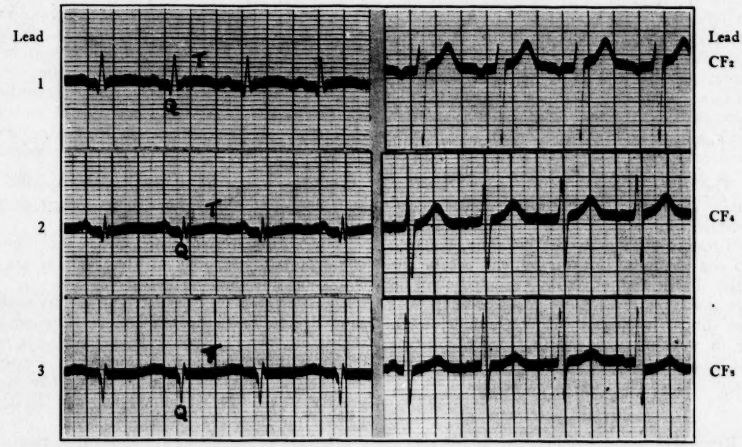

FIGURE 4. *Electrocardiogram Taken Slightly More Than Two Months after the Posterior Myocardial Infarction.*

apex posteriorly. There was slight tenderness in the left lower quadrant of the abdomen. The knee jerks were hypoactive, and the Babinski positive bilaterally.

and the protein 6.7 gm.; the chloride was 94 milliequiv. per liter.

On the evening of admission the patient coughed up thick orange-colored sputum for the first time,

culture of which revealed a few beta-hemolytic streptococci. A roentgenogram of the chest revealed increased density in both upper lobes and in the medial portions of both lower lobes; this showed some clearing four days later. The heart appeared normal. An electrocardiogram (Fig. 5) showed sinus tachycardia of 120, with low T waves in all leads. The QRS waves in Leads 1, 2 and 3 were low in voltage. This was not significantly different from a tracing taken nine months before, but wide Q waves had appeared in Leads CF_4 and CF_5. Six days later T_3 was slightly inverted.

The patient was treated with tourniquets, oxygen, morphine and Cedilanid, with some initial improvement. The temperature continued to rise, however, eventually reaching 104.8°F., with a pulse of 140 and respirations of 50. The serum nonprotein nitrogen rose to 110 mg. per 100 cc. The lung signs cleared considerably, but the patient became increasingly disoriented. An x-ray examination of the chest at that time revealed an enlarged heart with a rather diffuse haziness over both lung fields suggestive of pulmonary edema but with no frank area of pneumonia. His respirations became acidotic, and he died on the seventh hospital day.

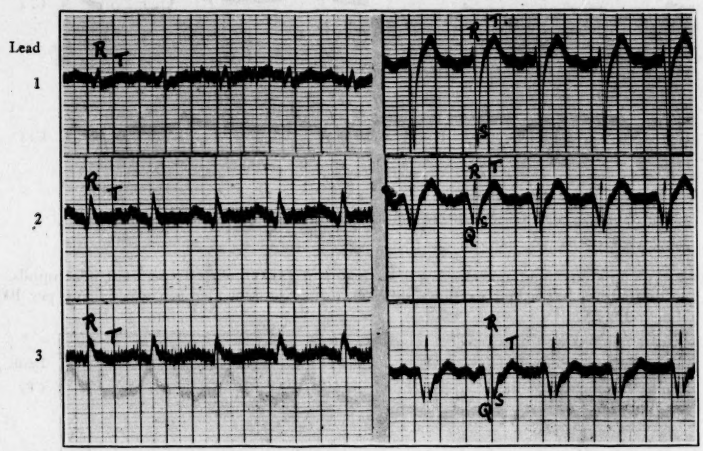

FIGURE 5. *Electrocardiogram Taken in 1944, the Year after the Second Attack and One Day after the Onset of the Final Illness.*

DIFFERENTIAL DIAGNOSIS

DR. REED HARWOOD: The first two admissions in this case can be summarized briefly. At the age of forty-nine, twenty months before death, this patient came into the hospital with a history, physical examination and electrocardiographic findings typical of a large anterior myocardial infarction. On the second admission, eight months later, the patient had a similar episode, the electrocardiograms being classic for posterior myocardial infarction. The only other thing worth mentioning in the initial admission is that he had a serum cholesterol of 292 mg., which is rather high.

Then we come to the final admission one year later. I should like to ask about the acidotic respirations. Since the man had rapid labored breathing on admission and some evidence of congestive failure, I should like to know how one can differentiate the type of breathing.

DR. ROBERT L. BERG: I saw the patient, and I believe that he had not only rapid and shallow respirations but also a uremic odor to his breath.

DR. HARWOOD: Then we have to qualify that statement. It might have been actual dyspnea, with a uremic odor to the breath.

I am also interested in the urinalyses. The only one reported was done at the time of the first admission, and that was negative.

DR. BENJAMIN CASTLEMAN: The urinary sediment showed 2 to 12 white cells and an occasional epithelial cell per high-power field. There was no albumin or sugar. On admission he had a +++ test for acetone, but that disappeared. The specific gravity was 1.034 on admission, and 1.020 and 1.024 after that.

DR. HARWOOD: May I ask about the urinary output during his final stay in the hospital?

DR. CASTLEMAN: You may look at the chart.

DR. HARWOOD: The output was 500 cc. in the first twenty-four hours, and rose to 1500 cc. on the fourth day; it was 1250 cc. on the next day, and fell off to 300 cc. on the last day.

The onset of pain on the final admission seemed to be similar in nature to the pain that he had had during the year previous to entry. It makes one think seriously of the possibility of his having had a third myocardial infarction. We might follow that line of reasoning and say that with this attack he went into congestive failure, that he developed edema of the lungs and diminished urinary output, with nitrogen retention, and that he had cerebral anoxia. That might have accounted for the positive Babinski and the increasing disorientation. We might go farther and say that he developed bronchopneumonia, which was responsible for the fever.

I think we ought to review the findings at the time of the last admission to see if there is anything against that diagnosis. The first thing is the dull pain over the right lower chest anteriorly. I do not consider this as being typical of the pain of myocardial infarction. I did consider the possibility of small pulmonary infarcts. In the examination of the heart I was surprised that he did not have gallop rhythm. This might have been present but not detected. I cannot explain tenderness in the left lower quadrant of the abdomen on the basis of recent myocardial infarction, and I do not know whether it is significant. I should think that the positive Babinski in a fifty-year-old man, even if he did have considerable anoxemia, is a rather unusual finding, and possibly one ought to consider some other lesion of the brain. The rise in the nonprotein nitrogen can reasonably be explained on the basis of the fall in blood pressure and a certain amount of nephrosclerosis. Concerning the culture of the sputum, I do not know whether the few beta-hemolytic streptococci have any significance. It must be considered, however, in the face of the high temperature. Curiously, the first chest film showed a normal-sized heart and a few days later another film showed an enlarged heart.

Perhaps this would be a good time to look at the films.

Dr. Maurice Fremont-Smith: How far apart were the examinations?

Dr. Laurence L. Robbins: Four days; but the last film was so poor that I did not put it up. The heart is probably enlarged in this film, but the film was taken anteroposteriorly instead of posteroanteriorly, and I am not impressed with the size of the heart. There is increased density in both upper lung fields and in the middle portions of the lower lung fields. These areas are clearer on the last film, but I still think that there is some increase in density; it is not particularly well defined, but there are mottled areas scattered throughout.

Dr. Harwood: Are they characteristic of any lesion?

Dr. Robbins: They could be pulmonary infarcts but they certainly are not typical; they could be caused by congestion.

Dr. Harwood: The electrocardiogram showed little change considering the pain. I do not set myself up to be an expert on this type of examination, but I believe that this patient had marked changes in the ST segment in the T waves in both of the previous attacks. If this were a fresh infarction, I should expect to see more than an inverted T_3 after six days. Will you comment on that, Dr. White?

Dr. Paul D. White: On the first admission in 1942 the record was absolutely characteristic of anterior myocardial infarction in both the limb leads and the precordial leads (Fig. 1). On the second admission, in 1943, a year before the patient died, he had absolutely typical evidence of posterior myocardial infarction superimposed on the changes due to the anterior scar (Fig. 2). It is interesting that he had heart block the second time; this is more frequently found after posterior myocardial infarction with thrombosis of either the left or the right circumflex vessel. The heart block cleared up entirely, as it usually does (Fig. 3). During his convalescence from the second myocardial infarct the electrocardiographic leads looked much better than after the first infarct. A neutralization of the "bad" features of the electrocardiogram that resulted from the first attack was effected by the second attack, even though there was actually more heart disease, for the reason that the T waves became upright again in both Lead I and in the precordial leads, as is shown in Figure 4, an electrocardiogram taken two months after the second attack. After posterior infarction the record never looks so "bad" as after anterior infarction, since inversion of T_3 may occur normally and does not appear so abnormal as inversion of T_1. The neutralization effect of the two lesions, front and back, was more or less maintained at the time of the last admission, and it becomes rather difficult to say from the electrocardiogram (Fig. 5) what happened at that time. Clinical evidence becomes all the more important because of this very difficulty. The limb leads show lower voltage without any especially acute changes in the T waves or ST segments but there is some change in the QRS waves, especially in Leads 2, 3, CF_4 and CF_5, and there is a simple tachycardia superimposed. The combination of lesions that had occurred before might explain the majority of the abnormalities in these last electrocardiograms. There were still fairly good precordial leads, except for the QRS waves in Leads CF_4 and CF_5 on the final admission, and the T waves and ST segments were better than those at the time of the other two admissions. One great difficulty is that, when one has coronary heart disease, anything that disturbs the circulation functionally can also cause changes in the electrocardiogram that are not necessarily due to structural damage.

Dr. Harwood: It seems to me that we have to decide whether this patient had a fresh infarction, with resulting congestive failure, and terminal bronchopneumonia, or whether he had some other event, such as infection or pulmonary infarction,

that by increasing the strain on the heart produced both coronary and myocardial failure. I am inclined to favor the latter, on the basis of the rather unusually high temperature and the rather minor signs or change in the electrocardiographic tracings.

Before closing I should like to mention two other possibilities that seem rather unlikely. One is a dissecting aneurysm, in which one would expect the blood pressure to stay much higher and the pain to be much worse. One would also expect to find evidence of circulatory changes in the extremities. I am going to exclude it. An extremely rare possibility is rupture of the heart through an aneurysm resulting from an old scar in the posterior part of the heart.* Ordinarily that produces sudden death, but I understand that occasionally there can be a slow leak. I simply mention it as a possibility, and I do not see how one can rule it in or out.

I also mention the possibility that mural thrombi were thrown off to the cerebral hemispheres and possibly to the mesentery, which would explain the positive Babinski, the increasing disorientation and the tenderness in the left lower quadrant of the abdomen.

DR. WHITE: It is quite possible that this final illness started with myocardial infarction. The symptomatology strongly suggests this, but I have never seen a death from myocardial infarction — and heart failure — with such a high temperature due to myocardial infarction alone. There was one change in the precordial leads† that I did not emphasize earlier, as I probably should have done, and that, in prominent form, was seen in the electrocardiogram at the last admission (Fig. 5), namely, deep Q waves in Leads CF_4 and CF_8. This may mean a new acute myocardial infarction, but my experience has not been sufficient in this particular for me to be absolutely sure of its presence or of its location.

CLINICAL DIAGNOSES

Coronary heart disease.
Cardiac failure.
Bronchopneumonia.

DR. HARWOOD'S DIAGNOSES

Coronary heart disease.
Cardiac failure.
Bronchopneumonia.
Pulmonary infarction?
Myocardial infarction, recent?

ANATOMICAL DIAGNOSES

Coronary thrombosis, old and recent.
Myocardial infarcts, old: left ventricle, anterior and posterior.
Myocardial infarct, recent, septal: left and right ventricles.
Mural thrombi, left and right ventricles.
Pulmonary infarcts.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed an enlarged heart, weighing 500 gm. There was an old anterior myocardial infarct, which was completely healed, and a posterior infarct, which was also healed. The coronary arteries showed old occlusions. There was, however, a recent occlusion in the descending branch of the left coronary artery, 2.5 cm. from its origin, as well as a large recent septal infarct involving both the left and the right ventricle, a most unusual occurrence. There were mural thrombi on both sides of the septum, those on the right apparently accounting for four large pulmonary infarcts in the right lower, right upper and left lower lobes. This is one of the few cases in which we can be fairly sure that the emboli arose from the right side of the heart, because careful examination of the leg veins revealed no thrombosis. Usually, even in the presence of mural thrombi in the right heart, we believe that such emboli come from the deep veins in the legs.

DR. WHITE: The chief clue in the electrocardiogram to the septal infarct was not in the limb leads but evidently comprised the deep Q waves in Leads CF_4 and CF_8; this finding was distinctly abnormal and had not been present before.

DR. CASTLEMAN: Because the current use of precordial leads in electrocardiography is not too well known, I have asked Dr. White to present a brief review of this subject.

*_Later comment by Dr. White._ I take issue with the statement by Dr. Harwood that the heart occasionally ruptures through an old scar. Rupture of the heart may occur through a fresh myocardial infarct, almost always within the first ten days or two weeks, but not through an old, healed and tough scar, even when there is a fairly well-marked cardiac aneurysm of long standing. Two recent papers emphasize this point.[9, 11] In a series of 270 cases of myocardial infarction found among nearly 3000 autopsies at the Massachusetts General Hospital from 1933 through 1940, there were included 165 cases of old infarction and 105 cases of fresh infarction. There were 10 cases of cardiac rupture in the whole series, but all were found among the cases with acute infarction. In the second paper, 47 cases of myocardial infarction were found in 115 consecutive autopsies carried out in patients in mental institutions in Massachusetts. Twenty-five of these cases showed old infarcts, and in none of these cases was there cardiac rupture; but among the 22 cases of recent infarction there were 16 with rupture of the heart. The difference between the incidences in the two series, which were 10 per cent and 73 per cent, respectively, was doubtless due to the fact that in the former there was, as a rule, adequate rest therapy during the process of healing, whereas in the latter there was little or none at all.

†During the last few years it has become customary at the Massachusetts General Hospital to take multiple precordial leads in any important or doubtful case, instead of the limb leads alone or the limb leads and Lead 4, which is the routine apical precordial lead. On rare occasions all six precordial leads, extending from C_1 (at the right of the sternum in the fourth interspace) to C_6 (the midaxillary line), are taken (see below). Generally, however, in the appropriate cases, as in the case cited here, the three routine precordial leads are taken that have been found to be the most helpful, namely, C_2 (with the electrode in the fourth interspace just to the left of the sternum), C_4 (with the electrode at the intersection of the midclavicular line and a line drawn from the C_2 point to the cardiac apex) and C_5 (in the anterior axillary line at the intersection of the horizontal line from the cardiac apex). These have been found, in the main, to be by far the most useful, and they are relatively simple to take. They demonstrate most of the changes underlying the lead points that concern the right ventricle and the anterior and lateral walls of the left ventricle. Lesions of the posterior wall of the left ventricle are not adequately shown by these lead points or by any others, except an esophageal lead.

In the case under discussion, Lead C_3 would probably have shown the greatest change, since it overlay the region of the septum. The letter C designates chest, and the letter F, which is added in the case discussion above, refers to foot and indicates that the left leg is the site of the indifferent lead point. If the right arm is used in the precordial leads, one speaks of CR, and if the left arm is used, one speaks of CL. On occasion Wilson's lead-point, off the body altogether but connecting all three extremities and called V, has been used as the indifferent point for the precordial leads. It (CV) gives the balance or average of the other three (CF, CR and CL).

DR. WHITE: Human electrocardiography began with chest leads; the first record ever published, and probably taken, was by Waller[1] in 1887, who placed one electrode on the front of the chest and one on the back. The capillary electrometer then used was exceedingly clumsy, and it was not until the string galvanometer was introduced in 1903 by Einthoven[2] that clinical electrocardiography became feasible.

In those early years it was the custom to take the limb leads, for convenience largely, but when certain electrocardiographers like Lewis[3] wanted to explore the thorax to get better records of auricular action, they did put electrodes over the heart, chiefly over the sternum in the region of the right auricle. In the course of time a number of investigators explored the chest, including Dr. Burwell and myself,[4] in the search for other planes than the frontal for determination of the projection of the electrical axis. Dr. Burwell and I wanted to study, for example, the electrical axis in space to get more idea of the size of the left ventricle. This did not pan out at the time because we did not appreciate the importance of the proximity of one of the electrodes to the heart itself.

As time went on, Wilson[5] in Ann Arbor and Wood[6] and Wolferth[7] in Philadelphia studied leads taken with electrodes placed on the chest directly over the heart. It has been found that direct leads from the heart itself show best the condition of the underlying myocardium and that next best are the leads taken from the chest wall as near as possible to the heart. Thus some ten or twelve years ago precordial electrocardiography began.

In the early days of clinical precordial electrocardiography its application was rather hit or miss; often just one electrode was applied and that, as a rule, was placed at the apex of the heart; in fact, this apical lead, with the other electrode placed on one of the extremities, became the recently current, and still customary, Lead 4. This apical lead has often been extremely helpful, being abnormal in some cases, especially those of coronary heart disease, in which the usual limb leads (Leads 1, 2 and 3) are normal, but such a finding is dependent on the proximity of the cardiac damage to the exploring electrode, whereas lesions elsewhere or abnormalities of the heart chambers other than that of the ventricle directly underlying the electrode are likely to be missed when only one single precordial lead (Lead 4) is taken.

During the last ten years a great deal of study has been carried out using multiple precordial leads, but much of this is still in the investigative stage. Precordial leads, however, have been numbered so that physicians will know about what the cardiologists are talking. The first precordial lead point is just at the right of the sternum in the fourth intercostal space. The second precordial lead point is just to the left of the sternum in the fourth intercostal space. The third precordial lead point is midway between the second and fourth on a direct line, the fourth being not necessarily the same as the routine Lead 4 but placed in the midclavicular line, usually in the fifth interspace on a line between the second precordial lead point and the cardiac apex. The fifth precordial lead point is on a horizontal line from the fourth in the anterior axillary line, and the sixth is in the midaxillary line. Other lead points have been suggested, such as a seventh in the posterior axillary line or at the angle of the left scapula and so forth, but we recognize officially only these six leads at the present time. The indifferent electrode, that is, the other electrode, can be placed either on the right arm (when we speak of the precordial leads as CR_{1-6}), on the left arm (when we speak of the precordial leads as CL_{1-6}), on the left leg (when we speak of the precordial leads as CF_{1-6}), or on a junction point of the three, Wilson's lead, in which the effect of any one extremity is neutralized by the others (when we speak of the precordial leads as CV_{1-6}). Thus, actually twenty-four precordial leads may be taken.

We have made a special study of about 175 cases, normal and abnormal, using these twenty-four precordial leads and have learned a good deal, but of course, they are not applied routinely. In fact, a good many cases need no precordial leads. In doubtful cases, especially those in which coronary insufficiency or massive pulmonary embolism is suspected, in cases of hypertension and coronary heart disease and for complete examination, precordial electrocardiography is in order.

Finally, we come to the practical application of these various precordial leads to clinical electrocardiography. Two reports have been published by the American Heart Association through its Committee for Standardization of Precordial Leads,[8,9] but neither of them is final because there has been no exact agreement concerning which precordial leads are to be advised. It is the consensus among experienced electrocardiographers that more than one precordial lead is important in order to see what is going on over the right ventricle, as well as over different parts of the left ventricle and the septum. In the last report of the American Heart Association three precordial leads were advised, namely, C_1, C_5 and C_6. We, however, and a number of others, have found that it is more practical and of greater value to use C_2, C_4 and C_6, which, as a rule, are located as follows: C_2 over the right ventricle, C_4 at the junction of the right and left ventricle, and C_6 over the left ventricle. It is astonishing how much difference there often is between C_4 and C_6 if C_4 is over the right ventricle and C_6 is over the left, or if one of these leads has a lesion directly underneath it. For the indifferent lead point we prefer the left leg. One is likelier to find abnormalities with that connection than with the others, although there are

occasions when a connection with the right arm or the left arm will be more useful. There is a scheme by which one can pick out the preferable lead, but it is complicated and for routine use during the past two years we have been using Leads CF_2, CF_4 and CF_5.

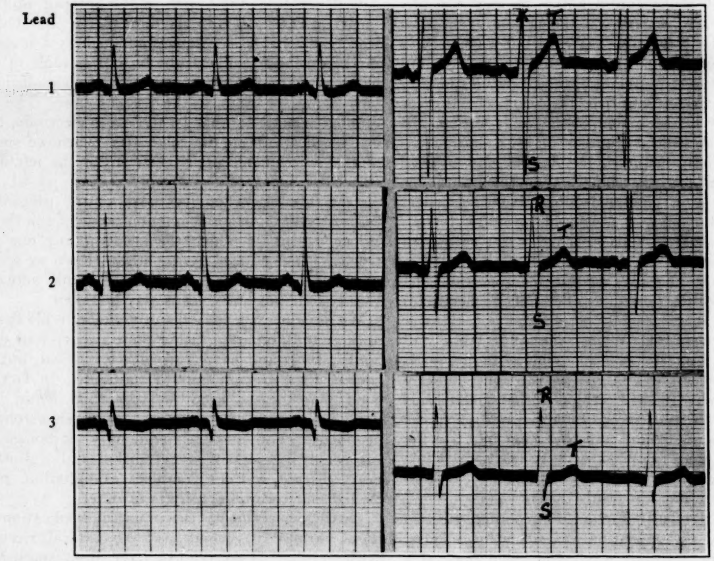

FIGURE 6. *Normal Electrocardiogram.*

Normally, in Lead CF_2 (Fig. 6), there tend to be a small R, a deep S and an upright T, which, however, may be fairly low. The P wave is unimportant, since it may be upright, inverted or diphasic. In Lead CF_4, R and S are frequently equal and there is a fair excursion of each. T is normally upright. In Lead CF_5, R becomes higher and S shorter in the average normal and T continues to be upright but is lower. It is only in Lead C_1 that T may be inverted normally in the adult; in young children one may find that the normal precordial T wave is inverted.

REFERENCES

1. Waller, A. D. Demonstration on man of electromotive changes accompanying heart's beat. *J. Physiol.* **8**:229-234, 1887.
2. Einthoven, W. Ein neues Galvanometer. Annalen der Physik, Folge IV, **12**:1059, 1903.
3. Lewis, T. Auricular fibrillation and its relationship to clinical irregularity of heart. *Heart* **1**:306-372, 1910.
4. White, P. D., and Burwell, C. S. Observations on electrical axis of heart. *Trans. Am. Soc. Clin. Invest.*, May 9, 1921.
5. Wilson, F. N. Distribution of potential differences produced by heart beat within body and at its surface. *Am. Heart J.* **5**:599-616, 1930.
6. Wood, F. C., and Wolferth, C. C. An electrocardiographic study of experimental coronary occlusion: inadequacy of three conventional leads in recording certain characteristic changes in action currents. *J. Clin. Investigation* **11**:815, 1932.
7. *Idem.* Electrocardiographic diagnosis of coronary occlusion by use of chest leads. *Am. J. M. Sc.* **183**:30-35, 1932.
8. American Heart Association and Cardiac Society of Great Britain and Ireland. Standardization of precordial leads. (First report.) *Am. Heart J.* **15**:107, 1938. Standardization of precordial leads. (Supplementary report.) *Ibid.* **15**:235-239, 1938.
9. American Heart Association. Second supplementary report by committee for standardization of precordial leads. *Am. Heart J.* **25**:535-538, 1943.
10. Friedman, S., and White, P. D. Rupture of heart in myocardial infarction. Experience in large general hospital. *Ann. Int. Med.* **21**: 778-782, 1944.
11. Jetter, W. W., and White, P. D. Rupture of heart in patients in mental institutions. *Ann. Int. Med.* **21**:783-802. 1944.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board
Joseph Garland, M.D. A. Warren Stearns, M.D.
Shields Warren, M.D. Dwight O'Hara, M.D.
C. Guy Lane, M.D. Chester S. Keefer, M.D.
William A. Rogers, M.D. Howard M. Clute, M.D.
Stephen Rushmore, M.D. Fletcher H. Colby, M.D.
Henry R. Viets, M.D. Robert L. Goodale, M.D.
Robert M. Green, M.D. Chester M. Jones, M.D.
Charles C. Lund, M.D. Harvey R. Morrison, M.D.

Associate Editors
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.
Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year (Boston funds); $8.52 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

DECELERATION IN MEDICAL EDUCATION

Since September, 1941, the medical schools of the United States, by operating on a nine-month schedule, have done their best to meet the dire national need that became clear so suddenly after the attack at Pearl Harbor. The same motivation brought about a similar acceleration in the educational programs of our hospitals, where the 9–9–9 plan of rotating internships locked into the medical-school schedules, and of our colleges and even high schools, where premedical courses were given. There are now two indications that the pressure on this educational system may be reduced: the Army has altered its contract with the medical schools in such a way that, until further notice, it will supply only 28 instead of 55 per cent of the matriculants, and the schools themselves are widely adopting the return to an annual period for the matriculation of future classes.

These moves on the part of the Army and of the medical schools call for rather prompt adjustments if future difficulties are to be avoided. They are not exactly movements in the same direction: the Army has reduced the number of its trainees but still calls for their continuous training and the medical schools have reduced the frequency of entering classes but are not yet in a position to return to a twelve-month basis. Unless the return to annual admission and a full-year course are made simultaneously and at the time — June — when courses formerly terminated, two things are bound to occur: first, for each year that the nine-month curriculum is retained, there will eventually be a delay of three months between medical-school graduations, with a maximum of a year, and second, when the twelve-month curriculum is resumed, the teaching schedules for three years will be chaotic. This brings up for immediate discussion, and for reasonably prompt decision, the question whether a return to the prewar timing of the curriculum is desirable.

This question has several phases. For the students at the top of the academic ladder, acceleration could be continued with profit and ease. These students can acquire in three years, as well as in four, the knowledge demanded, but there are not enough of them to supply the medical needs of the country — even in peacetime. The students at the bottom of the class in scholastic performance are definitely unable to complete the work satisfactorily in three calendar years, although many of them can do so in three and a half or four years. Many of these stable, hard-working students, who can do the work only if they are not hurried, have the attributes of character and personality that enhance their potential usefulness as physicians, and it is altogether proper that such persons be accorded some elasticity and consideration in the planning of the medical curriculum. The great majority of the students, however, stand in between these two ends of the academic ladder: they are the common denominators, they set the pace that the

others find too slow or too fast, and they determine and maintain the standard at which medical education should be conducted. They have been hard pressed by the accelerated curriculum, but they have risen to the occasion and are responsible for whatever success has attended the project.

But there is a time factor in the educational process for which even the stimulus of war cannot compensate. The physicist, the chemist, the physiologist, the pathologist, the clinician, all take account of time in their scientific and practical calculations. So the educator might devise some such formula as $(c+r+e)t$ to designate the quality of his product, c being the intellectual capacity of the student, r the resources of the school attended, e the effort devoted to the educational process by both the student and the faculty, and t the time during which these processes are in operation. Whatever the formula or the philosophy, time is an inevitable element.

The facts that formerly most medical students devoted some — and a few, all — of their summer vacations to medical pursuits, that the members of the faculties, because of diminishing numbers, have had to give even more time to teaching than that demanded by the nine-month year and that a nine-month internship does not meet the minimum requirements mean that the quality of medical education, other things being equal, must have deteriorated during the wartime acceleration of the curriculum. It was an emergency device, — "any port in a storm," — but it now appears that the storm has passed sufficiently for us to clear our decks again and to make our ship as stout and as seaworthy as possible. We are now planning to train the doctors of 1949 and later.

Are we to train them at the highest possible level and to meet the national and international responsibilities that we are now assuming? Before this question can be answered the time elements involved in the accelerated programs of our medical schools must be thoughtfully scanned by the medical, military and educational authorities of the Nation. The simplest method of deceleration would be to return to the annual type of curriculum and simultaneously to extend the 9–9–9 into a 12–12–12 plan for hospital internship. In the natural course of events this would bring about a gradual, not a sudden, return toward normal. If these changes were to be made effective as of June, 1945, the future classes to graduate from our medical schools would have the following medical-school increments, including vacations: Class of 1945, thirty-six months; Class of 1946, thirty-nine; Class of 1947, forty-two; and Class of 1948, forty-five. Furthermore, each graduate would have at least a twelve-month internship.

Continuation of the nine-month curriculum beyond June, 1945, can be justified only by two considerations: first, that there are values in the accelerated program that should be projected into peacetime and, second, that the national emergency is still acute enough to sacrifice quality for quantity in medical-school output in 1948 and 1949. Furthermore, if the latter consideration does hold, it seems likely that both the Army and the country in general would be benefited if the required number of physicians were obtained by increasing the percentage of Army matriculants rather than by retaining the accelerated schedule.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DION — Thomas J. Dion, M.D., of Quincy, died November 27. He was in his seventy-seventh year.

Dr. Dion received his degree from Laval University Medical Faculty, Montreal, in 1891. He was the oldest member of the Quincy City Hospital staff and had served as health commissioner and city physician in Quincy. He was a member of the American Medical Association.

His widow and a son survive.

O'NEIL — Richard F. O'Neil, M.D., of Boston, died November 30. He was in his seventy-first year.

Dr. O'Neil received his degree from Harvard Medical School in 1897. During World War I, he was commissioned a captain in the Medical Corps, serving as assistant to the surgeon-in-chief of the Department of Urology at Base Hospital No. 6 in France. He was promoted to major in 1918, and honorably discharged the following year. For several years he was private assistant to the late Dr. William M. Conant, outpatient surgeon at Carney Hospital and visiting surgeon at St. Elizabeth's Hospital. In 1911 he was appointed genitourinary surgeon in the Out Patient Department at the Massachusetts General Hospital. He was named visiting surgeon of the Genitourinary Service in 1915, and became chief of the service in 1917. He served as associate urologist at the Massachusetts General Hospital until 1934, when he was appointed to the board of consultation after reaching retirement age. He was well known at Harvard Medical School, where he was a member of the teaching staff. He was a member of the Boston and New England surgical societies and the American Medical Association and a fellow of the American College of Surgeons. He was a member of the American Urological Association, of which he was president from 1927 to 1928, as well as of the New England Section of the American Urological Association and the American Association of Genitourinary Surgeons, both of which he had served as president and secretary.

His widow and a son survive.

MISCELLANY

MILITARY AWARD TO DR. LYONS

Major Champ Lyons, M.C., A.U.S., associate in surgery and instructor in bacteriology and immunology, Harvard Medical School, and assistant surgeon, Massachusetts General Hospital (on leave of absence), has recently been awarded the Legion of Merit because, according to his citation, "he initiated and guided the methods by which the new and potent agent penicillin has been utilized in the treatment of the seriously wounded." His citation continues: "From the most forward mobile hospitals of Italy to the large general hospitals of the Interior, he personally operated upon and studied the treatment of the wounded, instructing his seniors and subordinates alike in a change of surgical procedures which is productive of better results. Lives and limbs of soldiers have been saved, and the disability and deformity of wounds materially reduced. His professional judgment, combining a basic knowledge of the science of bacteriology with skill and experience in practical surgery, has cast new light on the age-old problem of wound surgery. At no time has he spared himself mentally or physically, and the example he has set is an inspiration to all surgeons in the service."

MILITARY AWARD TO DR. MOORE

Major Merrill Moore, M.C., A.U.S., former associate in psychiatry at the Harvard Medical School and the Boston City Hospital, has been awarded the Bronze Star Medal by Major General O. W. Griswold, commanding officer of the Fourteenth Army Corps. This award made by direction of the President, reads: "For meritorious achievement in connection with military operations against the enemy in the South West Pacific."

In recommending Major Moore for this citation, his commanding officer said specifically:

> Your service at this base has been of the greatest benefit to the Government and to our war effort. Facing an immense problem, in your energetic and ingenious manner, you rapidly reduced the obstacle of psychoneurosis and related disorders in this area. As the only psychiatrist at that time, you immediately set about your assigned tasks with complete disregard for personal comfort and safety in your effort to solve existing difficulties. In addition to your regular hospital duties you devoted your personal leisure to consultations and lectures to all unit officers in this organization, often flying long distances to do so, so that they could understand and properly assist soldiers with emotional disturbances.
>
> Of the large number of cases called to your attention by line officers or referred to you for diagnosis and treatment by medical officers, a remarkably high percentage were returned promptly to effective duty and the majority of the remainder were returned shortly thereafter. In doing this you were always efficient, sympathetic, reasonable and constructive.
>
> Your performance of duty has been exceptionally meritorious. You have been a decided influence on the morale of our forces and an inspiration to the men with whom you have worked. You have strengthened cooperation and you have established confidence among officers and enlisted men as to the effectiveness of preventive psychiatry in the field as well as the value of mental hygiene for combat troops. Your actions contributed materially to the success of our combat operations.

NOTE

The following appointments to the teaching staff of Harvard Medical School have recently been announced: James Blanding Arey, of Minneapolis, Minnesota (S.B. University of Minnesota 1935, M.B. 1937, M.D. 1938 and S.M. 1940), instructor in pathology; Richard Colbert Cecil of Richmond, Virginia (A.B. Emory and Henry College 1925, M.D. Medical College of Virginia 1932), assistant in medicine; George Constantin Cotzias, of Canea, Greece, now working at the Massachusetts General Hospital, Boston (M.D. Harvard University 1943), assistant in neurology; Peter Hugh Forsham, of New York City (B.A. University of Cambridge 1937, M.A. University of Cambridge 1941, M.D. Harvard University 1943), research fellow in medicine; Lee Nathaniel Foster, of Oak Park, Illinois (S.B. Northwestern University 1938, M.B. 1940, M.D. 1942), assistant in pathology; George Erwin Gutmann, of Chapel Hill, North Carolina (M.D. University of Louisville 1943), assistant in pathology; David Milford Hume, of Muskegon, Michigan (S.B. Harvard University 1940, M.D. University of Chicago 1943), assistant in surgery; Edith Meyer, of Jamaica Plain (Ph.D. University of Leipzig 1933), research fellow in pediatrics; Robert Durant Ray, of Berkeley, California (A.B. University of California 1936, A.M. 1938, M.D. Harvard University 1943), assistant in orthopedic surgery; Eli Robins, of Rosenberg, Texas (A.B. Rice Institute 1940, M.D. Harvard University 1943), assistant in psychiatry; Daniel Sciarra, of Paterson, New Jersey (A.B. Harvard University 1940, M.D. 1943), assistant in neurology; Paul John Votta, of Providence, Rhode Island (A.B. Brown University 1936, M.D. Boston University 1941), assistant in roentgenology; and Philip Hulet Walker, of Minneapolis, Minnesota (S.B. Harvard University 1939, M.D. 1943), assistant in surgery.

BOOK REVIEWS

An Atlas of Anatomy. Vol. 1. *Upper limb, abdomen, perineum, pelvis and lower limb.* By J. C. Boileau Grant, M.C., M.B. Ch.B., F.R.C.S. (Edin.). 4°, cloth, 214 pp., with 227 illustrations. Baltimore: Williams and Wilkins Company, 1943. $5.00.

Those familiar with the author's *Method of Anatomy* (Baltimore: Williams and Wilkins Company, 1940) will not be surprised that this first volume of an atlas of anatomy, devoted to the upper limb, abdomen, perineum, pelvis and lower limb, is characterized by originality of approach and treatment and by perfection of technic. The 227 illustrations, of which nearly half are in two or more colors, are made from enlarged photographic positives of actual dissections, traced and then worked up by a competent artist. They are unusually lucid and true, and free from the confusion of too much detail. The labeling of structures is clear; the text intentionally slight. It is intended that the student should use Dr. Grant's *Handbook for Dissectors* and refer to the *Method of Anatomy* mentioned above for description and comment. When the second volume of the atlas shall be issued, this group of books may be heartily commended to student and practitioner alike.

An Introduction to Group Therapy. By S. R. Slavson. 8°, cloth, 352 pp. New York: The Commonwealth Fund, 1943. $2.00.

In the author's words, this volume "deals with a method of psychotherapy employed at the Jewish Board of Guardians of New York since 1934 and known as Group Therapy." The board serves underprivileged city children, boys and girls, who present "problems of personality" of the sort that "may manifest themselves in the form of delinquent or neurotic behavior." Service is rendered to boys and girls up to the age of eighteen.

Among these children, the majority of those who are selected for group therapy are under fourteen and apparently none are under eight years of age. Each therapeutic group consists, ideally, of five to eight children, who meet periodically with an older person known technically as the "group therapist." By their members the groups are called "clubs," and this word adequately suggests the spirit in which the meetings are conducted.

The book offers a comprehensive and detailed exposition of the practical and executive problems presented by such therapy. Emphasis is placed on the close and successful integration of group therapy with other social-service activities and with individual psychotherapy, including even individual child analysis. The presentation contains many excellent case histories and many vivid play-by-play accounts of what has occurred in specific group meetings.

The theoretical point of view that synthesizes and directs this wealth of otherwise probably bewildering and inchoate details and activities appears to be strongly and even predominantly psychoanalytic. This is apparent not only in the general orientation of the book but also in the use and even definition of specific terms. Thus one meets repeatedly the words "super-ego," "transference" and, less exclusively psychoanalytic, "ego," and one reads that "the chief charac-

teristic of the therapy group is its similarity to the family" and that the group therapist's, much like the psychoanalyst's, "chief function is to be a *neutral* person so that each . . . member of the group projects on the therapist his unconscious attitude toward adults."

On Growth and Form. By Sir D'Arcy Wentworth Thompson. 8°, cloth, 1116 pp., with 555 illustrations and frontispiece. New York: The MacMillan Company, 1943. $12.50.

This famous and monumental monograph, written during World War I and first published in 1917, has been out of print and extremely scarce for the past twenty years. The present edition has been revised and enlarged by its distinguished author as a *solacium ac perfugium* when active service was debarred him by his years. Much new material has been added. The chapter on rate of growth is double its original length; and the subjects of the bee's cell, the radiolarian skeleton, the mechanical construction of a bird, and Galileo's principle of similitude have been much extended. So unbounded is the writer's range of knowledge that scarcely any subject in biology is untouched. There is discussion, for example, of the fascinating problem of the left-handed snail shell and of the tetrakaidekahedral shape of cells in cell-aggregates, first noted by Joseph Plateau and Lord Kelvin and so beautifully demonstrated in this country by Dr. F. T. Lewis, of the Harvard Medical School.

Sir D'Arcy Thompson is a man of science who writes like a novelist; all the charms and merits of literary excellence and style are his. Moreover, so vast is his erudition that his volume is a treasury of apposite classic allusion and universal scientific reference. It is a work of perfect, total and utter scholarship, wherein the author, like Henri Fabre, the old man eloquent to whom he refers, "in his all but secular life has tasted of the first fruits of immortality."

Civilization and Disease. By Henry E. Sigerist, M.D., D. Litt., LL.D. 8°, cloth, 255 pp., with 52 illustrations. Ithaca, New York: Cornell University Press, 1943. $3.75.

The part played by disease in determining the progress and even the form of civilization is the fascinating subject that Dr. Sigerist discussed in the Messenger Lectures for 1940 and that he has further expanded in this delightful volume. Civilization is first presented as a factor in the genesis of disease, and in subsequent chapters, the relation of disease to economics, social life, law, history, religion, philosophy, science, literature and art is studied. Not less valuable than the factual matter are the glimpses that the reader gets of the author's philosophic assay of conditions and factors that, through the ages, have brought the world to its present pass, and he will be comforted by a final declaration: "The more I study history, the more faith I have in the future of mankind. . . . While we are struggling, the foundations are being laid for a new and better civilization."

The volume is excellently turned out, and is embellished by many beautiful reproductions of treasures from the world's museums. An excellent index gives quick guidance, whether one's interest be in "worms" or "Hitlerism."

Many a reader of this volume will find difficulty in laying it down unfinished, and will long for the leisure to browse among the sources of the allusions and references that are so lavishly spread before him.

Female Endocrinology. By Jacob Hoffman, M.D. 8°, cloth, 780 pp., with 180 illustrations. Philadelphia: W. B. Saunders Company, 1944. $10.00.

This book is an able exposition of the accumulated knowledge of endocrinology as it pertains to women. The book is really more than a review of female endocrinology, since it contains chapters on all the endocrine glands, in their relation not only to female physiology and pathology but also to general body physiology. This constitutes the reviewer's main criticism. To explain the mechanism and workings of all parts of the body a volume many times larger than this is needed, and in a book dealing with female endocrinology the pertinent relation of the nongenital glands to the genital glands should be sufficient. As a reference book it is good, since nearly all the important work of the last fifteen years has been included. Like all books on such a rapidly changing subject it cannot keep up with the times.

The careful explanation and the actual description of the technics for hormone determinations will be valuable to all workers in the field, especially those in laboratories in which such tests have not been performed. In the opinion of the reviewer this book is an excellent and able work on female endocrinology, but it should always be recognized that such a book is far from definitive.

Clinical Lectures on the Gallbladder and Bile Ducts. By Samuel Weiss, M.D. 8°, cloth, 504 pp., with 125 illustrations and 21 tables. Chicago: The Year Book Publishers, Incorporated, 1944. $5.50.

This is a nicely dressed book, well printed and well illustrated. It discusses diseases of the gall bladder and bile ducts in a series of twenty-nine clinical lectures. The method of approach makes for easy reading, introducing a certain degree of informality that is pleasant. At the end of each lecture is a bibliography, placing at the reader's disposal a great deal of pertinent modern literature. On the whole the volume is by no means exceptional, but on the other hand covers its subject adequately and in a practical manner that may appeal to many readers.

Handbook for the Medical Secretary. By Miriam Bredow. First edition. 8°, cloth, 253 pp., with 18 illustrations. New York: McGraw-Hill Book Company, Incorporated, 1943. $2.25.

Miss Bredow has produced an excellent handbook to be used as a guide to the conduct of a medical secretary or assistant. It deals with general information peculiar to the physician's office: patients, their records, filing, handling of appointments, accounts, correspondence and office procedure. The author also has included a brief description of various specialties of medicine, suggestions concerning the preparation of scientific manuscripts and a summary of the relation between the doctor and the law. A glossary of 2000 medical terms appears at the end.

If used with intelligent application, not as an irrevocable authority, this book will fill a much needed place as a textbook for the teacher and student of medical secretaryship as well as a reference book for those already holding such positions. It would be impossible for one small volume to be all inclusive since each chapter could overflow easily into a separate monograph and there is no vocation where such a variety of methods and experiences may be encountered as that of medical secretary.

Osler's Principles and Practice of Medicine. By Henry A. Christian, A.M., M.D., LL.D., Sc.D. (hon.), Hon. F.R.C.P. (hon., Can.). Fifteenth edition. 8°, cloth, 1498 pp. New York: D. Appleton–Century Company, Incorporated, 1944. $9.50.

The fifteenth edition of *Osler's Principles and Practice of Medicine* is off the press. In appearance and general make-up it follows previous models; the chief difference is that it is more Christian and less Osler than heretofore.

When medical textbooks are discussed, two divergent viewpoints are apparent: one claims that no single person can know enough of medicine to compose a useful book that is properly inclusive, and the other that one writer of wisdom and broad experience, particularly if he happens to be an assiduous student of medicine with an adroit pen, can produce a volume that is fully as informative, more evenly written and better balanced in use of space or material than any developed through polyandry.

This reviewer confesses that he belongs to the latter school. Thus he has enjoyed succeeding editions of *Osler*, — in part because of the very fact that they were written by one author, — always finding each one refreshing, agreeable to study and serviceable. The fifteenth is no disappointment.

Those who have been brought up on *Osler* will appreciate the ease with which the book can be read — a tribute to Dr. Christian's ability to carry on the Oslerian tradition as a writer; the references to pertinent literature, which come at the end of each section and are amazingly up to date — a tribute to Dr. Christian's ability to extract the meat from periodical literature as it accumulates; and the index at the end by which any topic from abasia to zinc poisoning can be located without difficulty — a tribute to good bookmaking.

Medical officers, wherever they may be, will be grateful for so much information that is recent and proved in regard to the diagnosis, prophylaxis and treatment of tropical diseases, in addition to all else that the book contains.

A curious error has crept into the "Contents," whereby diseases of the nose, larynx, bronchi, lungs, pleura, mediastinum and diaphragm are classified as diseases of the digestive system. Some day this may make of the first printing of this edition a collector's item as eagerly sought after as is the first printing of the first edition, in which the word "Georgias" appears.

Industrial Ophthalmology. By Hedwig S. Kuhn, M.D. 8°, cloth, 294 pp., with 114 illustrations, including 2 color plates. St. Louis: The C. V. Mosby Company, 1944. $6.50.

Industrial ophthalmology has, in this compact volume, its first compendium, drawn from the writings of many workers. It is illustrated by many plates, two of which are in color, and is well indexed. One is impressed by the author's grasp of the many ramifications in the field of industrial ophthalmology, and by her fairness in giving credits where they are due. Her implication is well taken that the text is not a completed subject, but that it is an expression of the present status of ophthalmology in industry.

The text consists of six chapters and an appendix. Five of the six chapters were written by the author; they deal with visual testing in industry, correction of visual defects, visual skills, protection of the eye in industry, and recent developments in industrial ophthalmology. The remaining chapter (Chapter IV) deals with industrial eye injuries caused by solid bodies, and it is a classic from the able pen of Dr. Albert C. Snell, of Rochester, New York. This chapter will serve as an excellent vade mecum for the ophthalmologist or physician interested in industrial medicine. The appendix lists toxic hazards to the eye and means of appraising loss of visual efficiency, which was reprinted by permission of the American Medical Association.

Tropical Nursing: A handbook for nurses and others going abroad. By A. L. Gregg, M.A., M.D., M.Ch., B.A.O. (Dublin), D.T.M. & H. (Lond.), L.M. (Rotunda Hospital). Second edition. 16°, cloth, 185 pp. New York: Philosophical Library, 1944. $3.00.

The subject matter of this little book goes far beyond nursing as such. The first section deals with hygiene for the tropics, and the second describes, very briefly, the more important tropical diseases and outlines their diagnosis and treatment. The third section is devoted to the technic of blood examination, blood transfusion, bowel lavage, the test meal, and intramuscular and intravenous injections. There follow advice on the care of the eyes, a glossary, a table of weights and measures, and an index.

Where medical services are inadequate in the tropics, nurses may be called upon to take responsibilities and to perform therapeutic procedures that are usually left in the hands of the physician. Some knowledge of the clinical picture of disease and of the accepted method of treatment helps a nurse to perform her functions intelligently. The reviewer believes, therefore, that this book will probably prove interesting and valuable to nurses who are taking assignments in the tropics for the first time.

Virus Diseases in Man, Animal and Plant: A survey and reports covering the major research work done during the last decade. By Gustav Seiffert. 8°, cloth, 332 pp. New York: Philosophical Library, 1944. $5.00.

This volume attempts to furnish a review of the present status of virus investigation. The bibliography is extensive, although the author states that he has mentioned only the most important works. The first part of the book deals with a general discussion of viruses. The major part is devoted to a consideration of certain and questionable virus diseases of man, mammals and birds. This is followed by a short section on viruses and new growths, pox of cold-blooded animals, virus diseases in insects, virus diseases in plants, virus-like organisms and filterable bacteria forms. The final section of the book is devoted to methods of virus investigation.

Since the book covers the major research work done on the subject during the past ten years, it should be of considerable value to research workers.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Internal Medicine in Dental Practice. By Bernard I. Comroe, M.D., associate in medicine, School of Medicine and School of Dentistry, University of Pennsylvania, and senior ward physician, Hospital of the University of Pennsylvania; Leon H. Collins, Jr., M.D., associate in medicine, University of Pennsylvania School of Medicine, instructor in medicine in the University of Pennsylvania School of Dentistry, and senior ward physician, Hospital of the University of Pennsylvania; and Martin P. Crane, M. D., instructor in medicine, School of Medicine, and School of Dentistry, University of Pennsylvania, visiting physician, Misericordia Hospital, Philadelphia, and lieutenant commander (MC), U.S.N.R. Second edition, enlarged and thoroughly revised. 8°, cloth, 543 pp., with 76 engravings and 6 colored plates. Philadelphia: Lea and Febiger, 1942. $5.50.

This valuable textbook for the dentist has been thoroughly revised in the light of the advances in the field of medicine since the publication of the first edition. Most of the sections have been completely rewritten, and a number of new illustrations have been added to the text. Two new sections have been added — one on focal infection and the other on sulfonamides, with special reference to sulfadiazine and its use by the dentist. The newer vitamins are described, and the sections on the cardiovascular system, the endocrines, the kidneys, the blood, the lungs and neurology have been expanded, with special reference to the oral manifestations or dental indications in these conditions. The book is well printed on good paper and should be in the office of every practicing dentist, as well as that of the internist.

The Psychology of Women: A psychoanalytic interpretation. By Helene Deutsch, M.D., associate psychiatrist, Massachusetts General Hospital, and lecturer, Boston Psychoanalytic Institute. With a foreword by Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School. Volume I. 8°, cloth, 399 pp. New York: Grune and Stratton, 1944. $4.50.

In this book the author draws on her extensive experience with women of all ages and includes in her text a great number of clinical histories. Trained by Freud and working closely with him for years, Dr. Deutsch is thoroughly grounded in the fundamentals of psychoanalysis. The purpose of the book is to explain the normal psychic life of women and their normal conflicts. She understands the behavior of adolescent girls, and her discussion of their life throws light on some of the troubles that the police are having with so-called "wayward girls." The author divides her text into three parts. The first has to do with the psychologic life of women from girlhood to womanhood, ending with the onset of menstruation. The second part discusses the three essential traits of femininity — narcissism, passivity and masochism. The third part considers the nonfeminine aspects of women, including homosexuality. The work ends with a chapter on the influence of the environment.

Synopsis of Diseases of the Heart and Arteries. By George R. Herrmann, M.D., Ph.D., professor of medicine, University of Texas, director of the Cardiovascular Service, John Sealy Hospital, and consultant in vascular diseases, United States Marine Hospital. Third edition. 12°, cloth, 516 pp., with 103 illustrations and 3 tables. St. Louis: The C. V. Mosby Company, 1944. $5.00.

The first edition of this manual was published in 1936, followed by the second in 1941. This third edition has been revised and the material rearranged. Corrections have been made in the text, and the material has been brought up to date. Old material has been condensed and in some cases removed, and new material, especially from war literature, has been added.

Aesculapius in Latin America. By Aristides A. Moll, Ph.D., secretary-editor of the Pan-American Sanitary Bureau, Washington, D.C., and consultant in tropical medicine to the Secre-

tary of War. 8°, cloth, 639 pp., with 179 illustrations. Philadelphia and London: W. B. Saunders Company, 1944. $7.00.

This valuable reference and source book on the history of medicine in the Latin-American countries of the Central and South American republics and in Mexico is greatly condensed but contains a great mass of material, reminding one of Fielding Garrison's *History of Medicine*. The text is divided into two parts — colonial times (1492 to 1808) and the Independence period (1809 to date). The treatment is principally topical, and many timely illustrations are scattered throughout the text. Two valuable tables are appended to the text — a chronology of diseases appearing in Latin America and a medical and general chronology (1492 to 1943). A bibliography of historical texts and indices of names and subjects conclude the volume. This is an essential text for all libraries, medical and general, and for all historians.

Laboratory Methods of the United States Army. Edited by James S. Simmons, M.D., Ph.D., D.P.H., Sc.D. (hon.), brigadier general, M.C., U.S.A., chief of the Preventive Medicine Service, Office of the Surgeon General, lecturer, Department of Preventive Medicine, Johns Hopkins University School of Medicine, lecturer in public health, Yale University School of Medicine, professorial lecturer in preventive medicine, George Washington University Medical School, and lecturer in tropical medicine, Army Medical School; and Cleon J. Gentzkow, M.D., Ph.D., colonel, M.C., U.S.A., and commanding officer, Deshon General Hospital, Butler, Pennsylvania. Fifth edition. 8°, cloth. 823 pp., with 103 engravings and 8 color plates, Philadelphia: Lea and Febiger, 1944, $7.50.

This composite work was first published as *Medical War Manual No. 6* and was written during World War I by officers of the United States Army. Since that time the manual has passed through four editions and has been enlarged at each appearance. This fifth edition has been revised throughout to bring it thoroughly up to date; many sections have been completely rewritten.

Guiding the Normal Child. By Agatha H. Bowley, Ph.D. With a foreword by D. R. MacCalman, M.D., Crombie-Ross Lecturer in Psychopathology, University of Aberdeen. 8°, cloth, 174 pp., New York: Philosophical Library, 1943, $3.00.

This small book describes the normal growth and development of children from birth to adolescence; it is of a popular character and designed for all persons interested in child guidance and the proper growth of children, and should be of interest to physicians. Emphasis is placed on the psychologic aspects and on the development of personality. The manual is divided into four periods of a child's life: infancy, preschool period, the middle years of childhood and adolescence. A chapter on children and the war concludes the volume.

The Letters of Doctor George Cheyne to Samuel Richardson (1733–1743). Edited, with an introduction, by Charles F. Mullett, Ph.D., professor of history, University of Missouri. Vol. XVIII. The University of Missouri studies: No. 1. 4°, paper, 137 pp., with 4 illustrations, and frontispiece. Columbia, Missouri University; University of Missouri, 1943.

This monograph reproduces eighty-seven letters written during the period 1733 to 1743 and copied into a notebook owned by Samuel Richardson and now in the University of Edinburgh library. The existence or whereabouts of the original letters are unknown. This work should be of interest to historians of medicine and should be added to history collections in medical libraries.

Rorschach's Test. Volume I: *Basic Processes*. By Samuel J. Beck, Ph.D., head of the Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago, and associate professor of psychology, Northwestern University. With a foreword by Willard L. Valentine, Ph.D., head of the Department of Psychology, Northwestern University. 8°, cloth, 223 pp. New York: Grune and Stratton, 1944. $3.50.

The intent in the present volume is to demonstrate the processes used in evaluating responses to the Rorschach test. The sole purpose is to provide students with a moderately steady frame of reference, with the hope that given such a manual of constant usage it will be possible to work with the test as a stable instrument.

Modern Medicine Annual—1943. 8°, cloth, 659 pp., with illustrations. Minneapolis: Modern Medicine, 1944.

This is a collection of abstracts in all fields of medicine and surgery, which are brought together for convenient reference. All were originally published in the periodical, *Modern Medicine*. They are grouped by subject. The latest developments in the use of penicillin, sulfonamides, hormones and vitamins are discussed. The newer procedures in the diagnosis and treatment of cardiac and gastrointestinal disorders are considered, as well as technics in every phase of surgery and orthopedics. There is a special division on military medicine and surgery in its various aspects, comprising thirty-two articles. The abstracts are short and well condensed, and provide a review of practical medicine and surgery as seen by the specialist in 1943. This manual should prove useful for ready reference purposes and should be in all medical libraries.

The Principles and Practice of Medicine, Originally written by Sir William Osler. By Henry A. Christian. M.D. LL.D., Sc.D. (hon.), F.R.C.P. (hon.) (Can.), clinical professor of medicine, Tufts College Medical School, and visiting physician, Beth Israel Hospital, Boston. Fifteenth edition. 8°, cloth, 1498 pp. New York: D. Appleton-Century Company, Incorporated, 1944.

This edition has been revised to place in the hands of the medical practitioner and Army and Navy personnel the most recent information brought to light since the publication of the preceding edition in 1942. Special emphasis is given to infectious and venereal diseases, tropical medicine and food deficiency disorders.

Textbook of General Surgery. By Warren H. Cole, M.D., professor and head of the Department of Surgery, University of Illinois College of Medicine, and director of Surgical Service, Illinois Research and Educational Hospitals, Chicago; and Robert Elman, M.D., associate professor of clinical surgery, Washington University School of Medicine, assistant surgeon, Barnes Hospital, associate surgeon, St. Louis Children's Hospital, and director of Surgical Service. H. G. Phillips Hospital, St. Louis. Fourth edition, 8°, cloth, 1118 pp., with 559 illustrations. New York: D. Appleton-Century Company, Incorporated, 1944. $9.50.

The first edition of this book was published in 1936 and it was thoroughly revised in 1941. This fourth edition has been brought up to date by the inclusion of new material throughout the text. New pages have been added to include more data on fluid and electrolyte balance of amino-acid therapy, hypoproteinemia, transfusion, chemotherapy and appendicitis. Increased emphasis has been placed on wounds, burns, surgical shock and other subjects related to war casualties. Despite the addition of new material the book has been kept the same size as the previous edition by the elimination of obsolescent material. A new chapter has been added, entitled "War and Catastrophe Surgery." Some of the illustrations have been improved and others have been replaced.

NOTICES

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

A meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Tuesday, December 19.

At 7:30 p.m. there will be a demonstration of clinical cases followed by the business meeting. Drs. David Cogan and Morton Grant will then speak on the topic "An Unusual Type of Keratitis Associated with Exposure to Butanol," and Dr. Theodore L. Terry on the subject "Pathology of Eyes following Maternal German Measles." These will be followed by a paper "The Myopia Paradox" by Dr. S. Judd Beach, including a discussion opened by Dr. Walter B. Lancaster.

SOUTH END MEDICAL CLUB

A regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, December 19, at twelve noon. Dr. E. Everett O'Neil will speak on the topic "The Treatment of Venous Thrombosis and Embolism." Dr. Samuel Grossman will preside.

Physicians are cordially invited to attend.

(*Notices continued on page xix*)